PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL

A THESIS SUBMITTED TO

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT (PUNJAB)

IN THE PARTIAL FULFILLMENT

FOR THE AWARD OF DEGREE OF

DOCTORATE OF MEDICINE

IN

NEPHROLOGY

MAY 2022

Submitted By

DR. GAURAV SINGLA

DEPARTMENT OF NEPHROLOGY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA, PUNJAB

DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled "**PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL**" submitted towards partial fulfillment of the requirements for the award of DM in Nephrology degree to BFUHS is a compilation of original work carried out by me under the supervision of Dr. Vikas Makkar, Professor & Head, Department of Nephrology, Dr. Bishav Mohan, Professor, Department of Cardiology and Dr. Simran Kaur, Associate Professor, Department of Nephrology. No part of this thesis has formed the basis for the award of any degree previously.

_____

DR. GAURAV SINGLA
Department of Nephrology,
Dayanand Medical College & Hospital,
Ludhiana, Punjab

Date:

Place:

CERTIFICATE OF SUPERVISORS

This is to certify that the work incorporated in this thesis entitled "**PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL"** has been carried out by Dr. Gaurav Singla under our direct supervision. The data incorporated in this thesis is original and genuine and has been carried out by the candidate himself.

Signature of Supervisor

Dr. Vikas Makkar
Professor & Head
Department of Nephrology
DMCH, Ludhiana

Signature of Co-Supervisor

Dr. Bishav Mohan
Professor
Department of Cardiology
DMCH, Ludhiana

Dr. Simran Kaur
Associate Professor
Department of Nephrology
DMCH, Ludhiana

Date:

ENDORSEMENT BY THE HEAD OF THE INSTITUTE

This is to certify that the thesis entitled "**PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL "** is a bonafide research work done by Dr. Gaurav Singla under the supervision of Dr. Vikas Makkar, Professor & Head, Department of Nephrology, Dr. Bishav Mohan, Professor, Department of Cardiology and Dr. Simran Kaur, Associate Professor, Department of Nephrology, in this institution.

Principal

Dr. Sandeep Puri
Principal
DMC&H, Ludhiana

Date:

COPYRIGHT

Declaration by the Candidate

I hereby declare that the Baba Farid University of Health Sciences, Faridkot, shall have the rights to preserve & use this thesis in print or electronic format for academic/study purpose by the research scholar/students.

Signature

Dr Gaurav Singla
Department of Nephrology,
Dayanand Medical College & Hospital,
Ludhiana, Punjab - 141001

Date:

© Baba Farid University of Health Sciences, Faridkot

Dedicated

to

my Family

&

Teachers

ACKNOWLEDGEMENT

Success is how high you bounce when you hit bottom.

- George S. Patton

*First and foremost, I bow in gratitude to the **Almighty God**, who showered His gracious blessings on me and imparted strength to accomplish this work.*

It is my proud privilege and pleasure to express my sincerest regards and deep sense of gratitude to my revered teacher and supervisor Dr. Vikas Makkar, Professor and head, Department of Nephrology, Dayanand medical college and hospital for his guidance, help, advice, inspiration, encouragement and continuous support, throughout my study period. His enthusiasm, integral view on research and his mission for providing high-quality work, has made a deep impression on me. Under his guidance I successfully overcame many difficulties and obstacles.

At this moment of accomplishment I am greatly indebted to my research Co-guide, Dr Bishav Mohan, Professor of Cardiology, and Dr Simran Kaur, Associate professor, Department of Nephrology, Dayanand medical college and hospital who offered me their mentor ship, love and care. This work would not have been possible without their guidance and involvement, their support and encouragement. Their zeal for perfection, passion, unflinching courage and conviction has always inspired me to do more. I sincerely thank all from the bottom of my heart and will be truly indebted to him throughout my life time.

My sincere thanks goes to Dr Preet Mohinder Sohal, Associate professor, Dr Suman Sethi Associate professor, Department of Nephrology, Dayanand medical college and hospital for guiding me through tough times and for providing constant and immense support.

My earnest thanks to my wife Dr Akanksha Garg for her valuable advice, constructive criticism, positive appreciation and teaching me to

laugh over daily hardships and sail through rough weather smoothly throughout my study.

My words will never be enough for my daughter Anaya whose hugs and smiles were my oasis, making me forget all my apprehensions.

I acknowledge the people who mean a lot to me, My parents, My father Mr. Jagdish Rai and My Mother Mrs. Nirmala , without their lifetime of hardwork and love, I would not have reached where I am today. I salute you for the selfless love, care, pain and sacrifice you did to shape my life. I am extremely thankful to my beloved sister Dr. Shaiffy and brother-in-law Dr. Rohit Kansal for their love and affection.

It's my fortune to gratefully acknowledge the support of my collegues Dr Abdul, Dr Sapna, Dr Rohan, Dr Tanish and Dr Abhinav for their invaluable suggestions and relentless efforts in shaping up my thesis.

My special thanks to Mr Naveen Bhatia and Mrs Namita Bansal from bottom of my heart, who helped me in compiling my thesis.

Dr Gaurav Singla

LIST OF ABBREVIATIONS

AAR	Age Adjusted Rate
AB	Aldosterone Blockage
ACE-Inhibitor	Angiotensin Converting Enzyme – Inhibitors
ACR	Albumin-to-Creatinine ratio
AKI	Acute Kidney Injury
ANCA	Anti-Neutrophilic Cytoplasmic Autoantibodies
ARBs	Angiotensin Receptor Blockers
ATN	Acute Tubular Necrosis
BP	Blood Pressure
CCB	Calcium Channel Blockers
CGN	Chronic Glomerulonephritis
CHF	Congestive Heart Failure
CI	Confidence Interval
CIN	Chronic Interstitial Nephritis
CKD	Chronic Kidney Disease
CKD-EPI	CKD Epidemiology Collaboration
CRIC	Chronic Renal Insufficiency Cohort
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
EF	Ejection Fraction
eGFR	estimated Glomerular Filtration Rate
ESKD	End Stage Kidney Disease
ESR	Erythrocyte Sedimentation rate
FSGS	Focal Segmental Glomerulosclerosis
GFR	Glomerular filtration rate
HF	Heart Failure
HOPE	Heart Outcome and Prevention Evaluation
HR	Hazard Ratio
HTN	Hypertension

KDIGO	Kidney Disease: Improving Global Outcome
KUB	Kidney Urinary Bladder
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
NSAIDs	Non-steroidal Anti-inflammatory Drugs
NKF-KDOQI	National Kidney Foundation- Kidney Disease Outcomes Quality Initiative
OR	Odds Ratio
RAAS	Renin-Angiotensin-Aldosterone System
RAS	Renin-Angiotensin System
RCT	Randomized Controlled Trials
SAVE	Survival and Ventricular Enlargement
SBP	Systolic Blood Pressure
SPSS	Statistical Package for Social Sciences
UPCR	Urine Protein Creatinine Ratio
USG	Ultrasonography

ABSTRACT

INTRODUCTION: Angiotensin converting enzyme inhibitors (ACE Inhibitors) and angiotensin receptor blockers (ARB's) are the best-studied antihypertensive agents that provide significant renal and cardiovascular protection for chronic kidney disease (CKD) patients. Recent studies suggest lack of evidence regarding the risk-benefit balance of ACE inhibitors/ARBs in patients with advanced CKD leading to their underutilization.

AIMS & OBJECTIVES: To study the Pattern and Outcome of use of ACE inhibitors and ARBs in CKD Patients.

METHODS: We conducted a prospective observational study on 100 CKD Stage 3 & 4 patients. The study population included 33 patients who were already taking either ACE inhibitors or ARBs at the time of enrolment and remaining 67 patients were the new patients those who were started on ACE inhibitors or ARBs as a part of their treatment from the time of their enrolment into the study. These were studied for pattern of use of these drugs and both these group of patients were followed for a period of 6 months to evaluate the tolerability to these drugs and to study the factors causing discontinuation among these patients.

RESULTS: Most common indication for use of ACE inhibitors or ARBs was proteinuric illnesses as compared to cardiac failure in CKD patients. Telmisartan was the most commonly prescribed drug. 62 % CKD patients were able to continue with the use of ACE inhibitors/ARBs for a period of 6 months. ACE inhibitors were better tolerated as compared to ARBs. CKD stage 3 patients also showed better tolerability. Most common adverse effect noticed were hyperkalemia followed by AKI. The overall mortality rate in our study was 16%. Patients with CHF and CKD stage 4 showed higher mortality.

CONCLUSION: The study reveals the underutilization of ACE inhibitors/ARBs in CKD patients. Tolerability and acceptability in CKD patients was better as compared to prevalence for use of these drugs in CKD patients. Tolerability of patients can be improved by a system of care that ensures regular checks of renal and cardiovascular function.

KEYWORDS:ACE inhibitors, ARBs, CKD, CHF, AKI

TABLE OF CONTENTS

S. NO.	TOPIC	PAGES
I	INTRODUCTION	1-6
II	AIMS AND OBJECTIVES	7
III	REVIEW OF LITERATURE	8-24
IV	MATERIALS AND METHODS	25-28
V	OBSERVATIONS AND RESULTS	29-59
VI	DISCUSSION	60-72
VII	LIMITATIONS	73
VIII	SUMMARY AND CONCLUSIONS	74-76
IX	BIBLIOGRAPHY	77-92
	APPENDICES – I - PROFORMA - MASTER CHART	
	APPENDICES – II - APPROVAL LETTER OF THESIS PLAN - THESIS PLAN	

LIST OF TABLES

Table No.	Title	Page No.
1.	DISTRIBUTION OF PATIENTS BASED ON USAGE OF ACE INHIBITORS/ARBs AT ENROLMENT	29
2.	AGE DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	30
3.	GENDER DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	31
4.	DISTRIBUTION BASED ON CKD STAGE IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	32
5.	DISTRIBUTION BASED ON CAUSE OF CKD IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	33
6.	INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	34
7.	DISTRIBUTION OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	35
8.	DISTRIBUTION OF INDIVIDUAL DRUG IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	36
9.	DURATION OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	37
10.	COMPLICATIONS OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	38
11.	AGE DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	39
12.	GENDER DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	40

13.	DISTRIBUTION BASED ON CKD STAGE IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	41
14.	DISTRIBUTION BASED ON CAUSE OF CKD IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	42
15.	INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT	43
16.	DISTRIBUTION OF ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT	44
17.	DISTRIBUTION OF INDIVIDUAL DRUGS IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	45
18.	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE AFTER ENROLMENT INTO THE STUDY	46
19.	DISTRIBUTION BASED ON ACE INHIBITORS/ ARBs USE IN THOSE ALREADY TAKING AND NEW PATIENTS STARTED AT ENROLMENT THOSE WHO CONTINUED THEM FOR 6 MONTHS	47
20.	DISTRIBUTION BASED ON CKD STAGE IN PATIENTS THOSE WHO CONTINUED ACE INHIBITORS/ARBs FOR 6 MONTHS	48
21.	DISTRIBUTION BASED ON INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	49
22.	DISTRIBUTION BASED ON TREATMENT OF CHF WITH ACE INHIBITORS/ARBs IN CKD PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	50
23.	DISTRIBUTION BASED ON ACE INHIBITORS OR ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	51
24.	DISTRIBUTION BASED ON CHANGE IN ACE INHIBITORS/ARBs DOSAGE IN PATIENTS THOSE WHO	52

	CONTINUED THEM FOR 6 MONTHS	
25.	DISTRIBUTION BASED ON ADVERSE EFFECTS OF ACE INHIBITORS/ARBs IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	53
26.	DISTRIBUTION OF PATIENTS BASED ON EVENT PRECEDING DISCONTINUATION OF ACE INHIBITORS/ARBs WITH DURATION LESS THAN 6 MONTHS	55
27.	CHANGE IN CKD STAGING IN THOSE WHO CONTINUED WITH USE OF ACE INHIBITORS/ARBs FOR 6 MONTHS	56
28.	DISTRIBUTION OF PATIENTS BASED ON CONCOMITANT BETA BLOCKER INTAKE WITH ACE INHIBITORS/ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	57
29.	MORTALITY DATA BASED ON INDICATION OF USE OF ACE INHIBITORS/ARBs IN CKD	58
30.	MORTALITY DATA BASED CKD STAGE AT THE ENROLMENT INTO THE STUDY	59
31.	PERCENTAGE OF PATIENTS USING ACE INHIBITORS/ARBs IN DIFFERENT STUDIES	62
32.	PERCENTAGE OF CKD PATIENTS WITH CHF USING ACE INHIBITORS/ARBs IN DIFFERENT STUDIES	64

LIST OF FIGURES

Fig. No.	Title	Page No.
1.	DISTRIBUTION OF PATIENTS BASED ON USAGE OF ACE INHIBITORS/ARBs AT ENROLMENT	29
2.	AGE DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	30
3.	GENDER DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	31
4.	DISTRIBUTION BASED ON CKD STAGE IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	32
5.	DISTRIBUTION BASED ON CAUSE OF CKD IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	33
6.	INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	34
7.	DISTRIBUTION OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	35
8.	DISTRIBUTION OF INDIVIDUAL DRUG IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT	36
9.	DURATION OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	37
10.	COMPLICATIONS OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT	38
11.	AGE DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	39
12.	GENDER DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	40

13.	DISTRIBUTION BASED ON CKD STAGE IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	41
14.	DISTRIBUTION BASED ON CAUSE OF CKD IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	42
15.	INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT	43
16.	DISTRIBUTION OF ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT	44
17.	DISTRIBUTION OF INDIVIDUAL DRUGS IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT	45
18.	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE AFTER ENROLMENT INTO THE STUDY	46
19.	DISTRIBUTION BASED ON ACE INHIBITORS/ ARBs USE IN THOSE ALREADY TAKING AND NEW PATIENTS STARTED AT ENROLMENT THOSE WHO CONTINUED THEM FOR 6 MONTHS	47
20.	DISTRIBUTION BASED ON CKD STAGE IN PATIENTS THOSE WHO CONTINUED ACE INHIBITORS/ARBs FOR 6 MONTHS	48
21.	DISTRIBUTION BASED ON INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	49
22.	DISTRIBUTION BASED ON TREATMENT OF CHF WITH ACE INHIBITORS/ARBs IN CKD PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	50
23.	DISTRIBUTION BASED ON ACE INHIBITORS OR ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	51
24.	DISTRIBUTION BASED ON CHANGE IN ACE INHIBITORS/ARBs DOSAGE IN PATIENTS THOSE WHO	52

	CONTINUED THEM FOR 6 MONTHS	
25.	DISTRIBUTION BASED ON ADVERSE EFFECTS OF ACE INHIBITORS/ARBs IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	54
26.	DISTRIBUTION OF PATIENTS BASED ON EVENT PRECEDING DISCONTINUATION OF ACE INHIBITORS/ARBs WITH DURATION LESS THAN 6 MONTHS	55
27.	CHANGE IN CKD STAGING IN THOSE WHO CONTINUED WITH USE OF ACE INHIBITORS/ARBs FOR 6 MONTHS	56
28.	DISTRIBUTION OF PATIENTS BASED ON CONCOMITANT BETA BLOCKER INTAKE WITH ACE INHIBITORS/ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS	57
29.	MORTALITY DATA BASED ON INDICATION OF USE OF ACE INHIBITORS/ARBs IN CKD	58
30.	MORTALITY DATA BASED CKD STAGE AT THE ENROLMENT INTO THE STUDY	59

INTRODUCTION

Kidneys are a pair of bean shaped organs on either side of the spine, below the ribs. Each kidney is about 4-5 inches long, roughly. As per current reports, nearly 10% of the population suffers from chronic kidney disease (CKD). The rate of prevalence is nearly 20% for people aged 65 and above.[1] While the major cause for the same has been attributed to an increase in the incidence of Type II Diabetes Mellitus, there have been some compelling evidence of major contributing factors in the early embryonic development.

Renal Physiology

It was postulated by Bowman in 1842, based on his anatomic study done that urine formation begins with glomerular secretion. Carl Ludwig, later on postulated glomerular filtration is followed by tubular reabsorption. Marshall confirmed tubular secretion in 1923, while filtration and reabsorption was confirmed by Wearn and Richards in 1924, thereby leading rapid advances in Renal physiology in the 20th century.[2] In the later years, concepts like “clearance” and “homeostasis” came into existence, having been introduced by van Slyke and Walter Cannon, respectively. Homer Smity, throughout 1930s and 1940s contributed to the Renal physiology, later on giving the most prestigious text “*The Kidney*”.[3]

The entire 20th century can be contributed to having been spent on the discovery and later on, more and more complex involvement of the Renin Angiotensin Aldosterone System (RAAS). Renin was discovered by Tigerstedt and Bergman in 1898, Angiotensin was discovered by Braun Menendez and Page in 1958. 21st century has brough remarkable insight into the important role of this regulatory system in kidney function. [4,5]

Epidemiology and Disease burden in India (and the World)

Several issues contribute to high prevalence of CKD in India. Nearly 28% of children are less than 2.5 kg, at birth, as per the data by

United Nations Children's Emergency Fund, the primary reasons for the same being hypovitaminosis and other nutritional deficiencies during pregnancy. Poverty, poor sanitation, majority of rural population, lack of diagnostic centres for majority of the population, overcrowding, water contamination, etc. add to the increase in glomerular and interstitial kidney diseases, with added factors like Diabetes and hypertension. By 2030, India is expected to have the largest population of diabetes in the whole world, which is a cause of concern, along with a substantial increase in the prevalence of patients with hypertension.[6,7]

India, with a population of more than 1 billion people, rise in the cases of CKD will definitely pose a threat to the healthcare and the economy in the future years. The estimated age adjusted rate (AAR) in India stands at approximately 229 per million people (pmp) with an annual increase of about 100,000 new people in the renal replacement programs in the country.[8-10] India has about 16% of the world population and is a lower-middle-income country. As of 2017, it was attributed that India has almost 115 million people affected by CKD, and 230,000 deaths due to CKD.[11-13] The million Deaths study documented a 50% increase in deaths caused by kidney failure in India between 2001 to 2003 and 2011 to 2013.[14]

CKD is a global health problem associated with considerable morbidity and mortality and despite advances in the treatment of end stage renal disease (ESRD) mechanisms to prevent and delay its progression are still being sought. CKD is defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated Glomerular filtration rate (GFR) < 60 ml/min/1.73m^2, that persists for more than three months.[15,16] Because of challenges in access to care in India, majority of the patients with advanced CKD are seen when eGFR is less than 15ml/min/1.73m^2.[17,18]

1.3 Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARB) in CKD

There are several evidence-based approaches, both pharmacologic and non-pharmacologic, to reduce or halt the progression of kidney disease even CKD and its related complications. They include lifestyle management, blood pressure and blood sugar control, the use of ACE inhibitors, lipid-lowering therapies, and other cardio-protective therapies.[16,19,20] Moreover, CKD patients are frequently refractory to conventional treatment and are at increased risk of adverse effects with hear failure medications.

ACE-Inhibitors/ARBs therapy is a cornerstone of hypertension and proteinuria management in CKD. They have been shown to have apparently salutary effects on markers of kidney function. They are the mainstays of therapy for hypertension, heart failure with reduced ejection fraction, and coronary artery disease.[21,22] Further, ACE-Inhibitors or ARBs have been recommended in patients with elevated albuminuria, due to their known cardio- and kidney-protective effects.[23,24] Given the change in the therapeutic landscape of hypertension and the public health burden of CKD, it seems reasonable to suggest that trends in ACE-Inhibitors/ARBs use in CKD population should be followed closely.[25] Although blockade of the RAAS with ACE inhibitors, angiotensin II type1 receptor antagonists, or the combination of both should be part of every strategy to slow progression of renal disease, a better understanding of the novel aspects of the RAAS should contribute to the development of innovative strategies not only to completely halt progression but also to induce regression of human renal disease.[26] The RAAS plays a pivotal role in many of the pathophysiological changes that lead to progression of renal disease. Traditionally RAAS was considered as an endocrine system and its principal role was to maintain blood pressure (BP). In recent years local RAAS has been described to operate independently from systemic and local angiotensin II in the kidney to contribute to hypertension and kidney damage. Although ACE-I s and ARBs have

shown to be quite promising, there have been cases of them leading to the reduction of GFR, following their initiation, further leading to an increased risk of hyperkalaemia and acute kidney injury.[27-29]

In patients with early to moderate CKD, Renin Angiotensin System (RAS) inhibition has been the choice of care, however, there have been concerns and lack of consensus regarding the use of RAS inhibitors in advanced CKD, with many physicians still being reticent to prescribe such therapy, even though many studies have suggested it to be safe and effective in advanced CKD.[24,30]

Little has been done to assess the pattern of discontinuing ACE-Inhibitors/ARBs across the spectrum of kidney function in real-world clinical practice. Existing data on the rates of ACE-Inhibitors/ARBs discontinuation largely originated from clinical trials.[31]

1.3.1 Mechanism of Action

The mainstay of treatment in patients with glomerular diseases is the use of ACE inhibitors and/or ARBs. They result in the decline in the GFR and reduction in proteinuria. The use of RAAS inhibitors leads to the prolongation of graft survival in patients.[32,33]

Angiotensin II causes direct vasoconstriction of precapillary arterioles and postcapillary venules, inhibits the reuptake of norepinephrine, stimulates the of sodium and water, stimulates synthesis and release of aldosterone, and stimulates hypertrophy of both vascular smooth muscle cells and cardiac myocytes.[34,35]

The exact mechanism of ACE inhibitors is not fully known. They interfere with the RAAS, but their effect is not directly related to renin levels in the blood. As the name implies, ACE inhibitors block an angiotensin-converting enzyme that converts angiotensin I to angiotensin II. Decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodelling of smooth muscle and cardiac myocytes. Lowered arterial and venous pressure reduces preload and afterload. Also, the hypothesis is that ACE

inhibitors interfere with the degradation of bradykinin, a peptide that causes vasodilation.[36]

ACE inhibitors effectively reduce proteinuria by approximately 50%.[37] Sodium balance is an important determinant of the antiproteinuric efficacy; the latter is virtually abolished when there is a liberal sodium intake[38] but is restored by dietary sodium restriction and/or concomitant use of a diuretic. Dietary protein restriction also increases the antiproteinuric effect.

The benefits of strict BP control in slowing kidney disease progression have been demonstrated in several clinical trials and the question whether specific agents like ACE inhibitors and ARBs provide reno-protective benefits beyond BP lowering is to be answered. Several studies support these agents reduce proteinuria and protect renal function, whereas the opposite is stated by others.[39] Definitive data on whether to continue use of ACE inhibitors and ARBs in patients with CKD is lacking.[40] At this time, it is difficult to prove that the Reno protective effects of RAAS inhibitors are separate from their antihypertensive effects. ACE inhibitors and ARBs are indicated for use in CKD patients with hypertension and proteinuria/ albuminuria.[41] The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) *Clinical Practice Guidelines on Hypertension* currently state that with careful monitoring most patients with advanced CKD can continue taking ACE-inhibitors/ARBs.[42] In a study to find the trends in Angiotensin-Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker Use among those with impaired kidney function in the United States, Murphy and others found that rates of ACE/ARB use increased in the early 2000s among United States adults with CKD, but for unclear reasons, use appeared to plateau in the ensuing decade. They stated that Research examining barriers to care and other factors is needed.[43] The need of this study was also based on the observation that data on Prevalence and practice of use of ACE Inhibitors and ARBs in CKD patients and outcomes of its use is not much available in Indian population.

To find the exact pattern of use and tolerability of CKD patients to use of these drugs, this study was being undertaken.

AIMS AND OBJECTIVES

1. To study the pattern of use of ACE inhibitors and ARBs in CKD Patients
2. To study the outcomes of use of ACE inhibitors and ARBs in CKD patients

REVIEW OF LITERATURE

ACE-Inhibitors and ARBs are recommended by multiple clinical guidelines in patients with elevated albuminuria due to their cardio- and kidney-protective effects.[21,23] Albuminuria is defined as urine albumin-to-creatinine ratio (ACR) > 30 mg/g and is a pathologic condition reflecting kidney damage. Adverse kidney events like end-stage kidney disease, decline in eGFR, and acute kidney injury are usually the associated risk factors related with increased albuminuria.[44-47]

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest use of an ACE-Inhibitor or ARB as an antihypertensive agent *"in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours"* and *"in both diabetic and non-diabetic adults with CKD and urine albumin excretion > 300 mg/24 hours"*. Similarly, the American Diabetes Association suggests that *"in non-pregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine".*[48]

In a study by **Maschio G *et al*** in 1996 to determine the effect of the angiotensin-converting–enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases. In a three-year trial involving 583 patients with renal insufficiency caused by various disorders, 300 patients received benazepril and 283 received placebo. The underlying diseases included glomerulopathies (in 192 patients), interstitial nephritis (in 105), nephrosclerosis (in 97), polycystic kidney disease (in 64), diabetic nephropathy (in 21), and miscellaneous or unknown disorders (in 104). The severity of renal insufficiency was classified according to the base-line creatinine clearance: 227 patients had mild insufficiency (creatinine clearance, 46 to 60 ml per minute), and 356 had moderate insufficiency (creatinine clearance, 30 to 45 ml per minute). The primary end point

was a doubling of the base-line serum creatinine concentration or the need for dialysis. They concluded that benazepril provides protection against the loss of renal function in patients with chronic renal insufficiency caused by various disorders. This protective effect was associated with a substantial decrease in blood pressure and urinary protein excretion.[49]

A meta-analysis was done by **Giatras I *et al*** in 1997 using the MEDLINE database for studies on the effects of ACE inhibitors on renal disease from 1977 to 1996. A total of 1,594 patients in 10 studies were included in the analysis. Most patients were men (range, 48% to 77%), and the mean age ranged from 44 to 66 years. Mean baseline impairment of renal function was mild in three studies (mean serum creatinine level, 1.0 to 1.8 mg/dL), moderate in five studies (mean serum creatinine level, 2.1 to 3.0 mg/dL), and severe in two studies (mean serum creatinine level, 4.2 to 4.4 mg/dL). Enalapril was used in seven studies, and captopril, cilazapril, and benazepril were used in one study each. The control groups received placebo in four studies, β-adrenergic blockers in three studies, calcium-channel blockers in two studies, and an unspecified combination of antihypertensive agents in one study. The reported relative risk for end-stage renal disease ranged from 0.51 to 3.36 and was not significant in any single study. However, the pooled relative risk was 0.70 (CI, 0.51 to 0.97), indicating a statistically significantly lower risk for development of end-stage renal disease in the ACE inhibitor group. The result of the test for heterogeneity of relative risk among studies was not significant ($P < 0.75$ and >0.5), indicating that treatment effect did not significantly differ among studies.[50]

A study was conducted by **Mann J *et al*** under the name of The Heart Outcome and Prevention Evaluation (HOPE study) in 2001. 980 patients with mild renal insufficiency (serum creatinine concentration ≥ 124 mmol/L [≥ 1.4 mg/dL]) and 8,307 patients with normal renal function (serum creatinine concentration < 124 mmol/L [≥ 1.4 mg/dL]), were included in the study. Cardiovascular and all-cause mortality rates

were nearly twice as high in patients with renal insufficiency (Hazard ratio; HR, 1.90 [95% CI, 1.53 to 2.36] and 1.83 [CI, 1.54 to 2.17], respectively, by Cox regression controlling for ramipril use; P < 0.001 for both comparisons), as were hospitalizations for heart failure (HR, 2.11 [CI, 1.56 to 2.81]; P < 0.001).[51]

Tokmakova MP *et al* did a prospective study on Survival and Ventricular Enlargement (SAVE) trial subjects in 2004. A total of 2,183 subjects were chosen for the study. SAVE was a randomized trial of captopril versus placebo in 2,231 patients with acute MI (3 to 16 days) and LVEF <40%. The mean eGFR from the 2,183 SAVE subjects was 70.0+/-20.7 mL/min/1.73 m^2.Subjects with lower eGFR were older, were more likely to be women, and had higher serum creatinine concentrations. Subjects with lower eGFR also had more comorbidity, as assessed by a higher incidence of hypertension, diabetes, prior MI, and history of heart failure. eGFR was significantly associated with a higher risk for all cardiovascular (CV) events (linear tests for trend, P<0.001 for all outcomes). Even mild reductions in eGFR (60 to 74 mL/min/1.73m^2, relative to 75 mL/min1/1.73 m^2) were associated with a significantly increased risk for total mortality, CV mortality, and the combined CV mortality and morbidity outcome. The relative risk reduction due to captopril was nominally higher in subjects with CKD (31% *versus* 20%). Nevertheless, the interaction between study drug and CKD was not statistically significant (P=0.29).[52]

In a study by **Hou FF *et al*** in 2006, they assessed the efficacy and safety of benazepril in patients without diabetes who had advanced renal insufficiency. They enrolled 422 patients in a randomized, double-blind study. After an eight-week run-in period, 104 patients with serum creatinine levels of 1.5 to 3.0 mg per decilitre (group 1) received 20 mg of benazepril per day, whereas 224 patients with serum creatinine levels of 3.1 to 5.0 mg per decilitre (group 2) were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. All patients received conventional antihypertensive therapy. The

primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. In their study they concluded that benazepril therapy was associated with a significant improvement in renal outcome and surpassed that attributable to blood-pressure control in patients without diabetes who had advanced renal dysfunction.[24]

Berger AK *et al* in the year 2007 did a retrospective study on patients with CKD along with cardiovascular disease. A total of 4,573 patients were identified and included in the study. The mean age of the cohort was 69.1 years. The GFR was >90 mL/min in 469 (21.7%), 60 to 89 mL/min in 546 (25.1%), 30 to 59 mL/min in 773 (35.6%), 15 to 29 mL/min in 238 (11.0%), and <15 mL/min in 143 (6.6%).The in-hospital use of ACE inhibitorts declined with worsening renal function with a steep cut-off among patients who had a GFR < 30 mL/min. ACE inhibitors were administered during hospitalization to 319 patients (68.0%) with a GFR >90 mL/min and to 157 patients (42.3%) with a GFR <30 mL/min. The increased use of ARBs (11.3%) in patients with worse renal function partially offset the lower use of ACE inhibitors in this group. Renal function did not appear to have any impact on the in-hospital prescription of β-blockers. Glomerular filtration rate was strongly associated with mortality, whether measured during hospitalization, at 30 days, at 6 months, or at 1 year. The fully adjusted 30-day mortality was lower among patients who received ACE inhibitors or ARBs compared to those patients who received neither therapy. There was no interaction between severity of renal dysfunction and use of ACE inhibitors or ARBs.[53]

A prospective study was conducted by **Onuigbo MA *et al*** (2008) to analyse the course of eGFR following withdrawal of aldosterone blockade (AB) with ACE inhibitors and ARBs in 100 CKD patients. The mean follow up period of patients was 26 months. They observed that sixteen patients progressed to ESRD, of whom seven

died. In 74, eGFR improved from 23.9±9 to 39.2±15.4 ml/min/1.73 m^2 BSA (P=0.001). The majority of the cohort, 95 patients, had known risk factors: 26 with RAS, 12 hypovolemia, 11 sepsis, 10 NSAIDs/cox II inhibitor use/abuse, 7 CIN (chronic interstitial nephritis), 2 congestive heart failure, 2 obstructive uropathy, and 27 with other medical and surgical causes, including malignancies, postoperative states, and infections. In the 26 with RAS, 5 with higher baseline creatinine 2.1±0.6 versus 1.5±0.4 mg/dl, progressed to ESRD; 4/5 ESRD patients died after 6.3 months. The remaining five patients demonstrated sustained improved eGFR with discontinuation or reduction of RAAS blockade, despite normal renal arteries and the absence of known traditional risk factors. Uric acid/Creatinine generally increased following withdrawal of AB (aldosterone blockers). They concluded that worsening azotemia in older susceptible CKD patients on AB, often but not always associated with known precipitating risk factors remains under-recognized. Sustained improved eGFR often follows the discontinuation of AB.[54]

In a study **Kolesnyk I *et al*** in 2010, they found that drugs that inhibit the RAS are proven to be effective in the treatment of hypertension and heart failure. In patients with CKD these medications appeared to bring benefit beyond their direct effects on the cardiovascular system, resulting in preservation of renal and peritoneal function and improved patient survival.[55]

An observational report of 52 patients was presented by **Ahmed AK *et al***, in 2010. These were the patients referred to the Low Clearance Clinic, with an average eGFR of about 16.38 mL/min/1.73m^2 at presentation to the clinic. The median follow-up of the patients was about 30 months. When the ACE inhibitors/ARBs were stopped, there was a substantial increase in the eGFR, which rose from initial presentation of 16.38 to 26.6 mL/min/1.73m^2.This increase in eGFR was seen in nearly 61.5% of the patients.[56]

In a study by **Ahmed A *et al*** in 2012 to study the Renin-angiotensin inhibition in systolic heart failure and CKD. Of the 1,665

patients (aged ≥65 years) with systolic heart failure (ejection fraction <45%) and CKD (eGFR <60 mL/min/1.73 m^2), 1046 received ACE inhibitors or ARBs. Propensity scores for the receipt of these drugs, estimated for each of the 1,665 patients, were used to assemble a matched cohort of 444 pairs of patients receiving and not receiving these drugs who were balanced on 56 baseline characteristics. In their study they found that Discharge prescription of ACE inhibitors or ARBs was associated with a significant modest reduction in all-cause mortality in older patients with systolic heart failure with CKD, including those with more advanced CKD.[57]

In another study done by **Ahmed A *et al*** (2012), they selected patients with diastolic heart failure (ejection fraction ≥ 45%) and CKD (eGFR < 60 mL/min/1.73m^2). Out of 1,340 old patients with heart and kidney disease, 717 patients had received either ACE inhibitors or ARB or both. A cohort of 421 patients were prepared, receiving, and not receiving drugs, and were matched from various characteristics. 558 patients received ACE inhibitors, 147 received ARBs, and 12 received both. The patients were also grouped into below-target and target dose receiving patients with outcomes using patients not receiving drugs as outcomes, based on other studies done in cardiology.[58]Among matched patients with diastolic heart failure and CKD, a discharge prescription for ACE inhibitors or ARBs was associated with an 11-month longer (41 *vs* 30 months for those not receiving those drugs) median survival, corresponding with an 18% relative risk reduction (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.70-0.97; P =0.021). Of the 309 (73% of 421) matched patients with data on doses, 92 (22%) received target and 217 (51%) received below-target doses of these drugs. HRs for total mortality associated with the use of below-target and target doses were 0.82 (95% CI, 0.67-1.00; P =0.051) and 0.84 (95% CI, 0.63-1.11; P = 0.224), respectively. Patients receiving ACE inhibitors or ARBs had a 6% higher absolute risk and approximately 7 months longer median time to heart failure hospitalization (HR, 0.98; 95% CI, 0.82-1.18; P = 0.816). Patients

receiving RAS inhibitors had a 1% lower relative risk and 3 months longer median time to all-cause hospitalization (HR, 0.81; 95% CI, 0.70-0.94; P = 0.005).[59]

In a study by **Molnar MZ *et al*** in 2014, they conducted a study to assess the association between ACE inhibitors/ ARBs use and mortality in patients with CKD. A logistic regression analysis was used to calculate the propensity of ACE inhibitors/ARBs initiation in 141,413 U.S. veterans with non-dialysis CKD who were previously unexposed to ACE inhibitors/ARBs treatment. They examined the association of ACE inhibitors/ARBs administration with all-cause mortality in patients matched by propensity scores using the Kaplan-Meier method and Cox models in "intention-to-treat" analyses and in generalized linear models with binary outcomes and inverse probability of treatment weights in "as-treated" analyses. They found that in non-dialysis-dependent patients with CKD, ACE inhibitors/ARBs administration was associated with greater survival.[60]

A prospective cohort study was done by **Hsu TW *et al*** in 2014 to assess the effectiveness and safety of ACE inhibitors/ARBs use for advanced predialysis CKD in patients with hypertension and anaemia. 28,497 hypertensive adult patients with CKD who fulfilled the inclusion criteria were selected for the study. In a median follow-up of 7 months, 20,152 patients (70.7%) required long-term dialysis and 5,696 (20.0%) died before progression to end-stage renal disease requiring dialysis. They observed that the use of ACE inhibitors/ARBs was associated with a lower risk for long-term dialysis or death. The renal benefit of ACE-Inhibitors/ARBs use was consistent across most patient subgroups, as was that of ACE-Inhibitors or ARBs monotherapy. Compared with nonusers, the ACE-Inhibitors/ARBs users had a higher hyperkalemia associated hospitalization rate, but the risk of pre-dialysis mortality caused by hyperkalemia was not found to be significantly increased. They concluded that patients with stable hypertension and advanced CKD who receive therapy with ACE-Inhibitors/ARBs exhibit

an association with lower risk for long-term dialysis or death by 6%. This benefit does not increase the risk of all-cause mortality.[30]

In a study by **Dattolo PC *et al*** in 2016 to study the Conservative management of CKD stage 5, they tested the role of ACE-Inhibitors in slowing the progression of renal damage in a real-world elderly population with CKD stage 5. They found that proteinuria independently predicts further renal damage progression even in end-stage renal disease patients not yet in dialysis. In cohort of elderly patients with very advanced CKD, ACE inhibitors were effective in slowing down further renal damage progression.[61]

In a study by **Frohlich H *et al*** in 2016 to study Long-term changes of renal function in relation to ACE inhibitor/angiotensin receptor blocker dosing in patients with heart failure and CKD. In this retrospective observational study, they identified 722 consecutive patients with systolic CHF, stable CKD stage III/IV and chronic ACE-Inhibitors/ARBs treatment from the outpatient heart failure clinics at the Universities of Hull, UK, and Heidelberg, Germany. Change of renal function, worsening CHF, and hyperkalaemia at 12-month follow-up were analysed as a function of both baseline ACE-inhibitors/ARBs dose and dose change from baseline. In patients with systolic CHF and stable CKD stage III/IV, neither continuation of high doses of ACE-inhibitors/ARBs nor up-titration was related to adverse changes in longer-term renal function. Conversely, down-titration was not associated with improvement in eGFR. They concluded that use of high doses of ACE-inhibitiors/ARBs and their up-titration in patients with CHF and CKD III/IV may be appropriate provided that the patient is adequately monitored.[62]

In a study by **Lin CC *et al*** in 2017 to study the ARBs are associated with lower mortality than ACE inhibitors in predialytic stage 5 CKD and their study demonstrated the difference in the effectiveness and safety between ACE inhibitors, ARBs and dual RAS blockade therapy (ACE inhibitors plus ARBs) in pre-dialytic stage 5 CKD

patients. As compared with ARBs, dual blockade with ACE inhibitors and ARBs showed a higher risk of death and composite endpoint of long-term dialysis or death in diabetic subgroup as well as a higher rate of hyperkalaemia-associated hospitalization in non-diabetic subgroup, and ACE inhibitors were associated with a higher risk of death, especially in diabetic subgroup. Monotherapy of RAS blockade, especially ARBs, was more effective and safer than dual RAS blockade in pre-dialytic stage 5 CKD patients.[63]

Liu Y *et al* (2017) did a meta-analysis to understand the effects of ACE inhibitors and ARBs on residual kidney functions in the dialysis patients. They identified relevant studies from MEDLINE and EMBASE from 1950 to December 2016. The studies were limited to randomized control trials (RCT). A total of 11 RCTs with 1,856 patients were included for the final analysis. Data regarding the effects of ACE inhibitors/ARBs on renal function were available from 5 trials[64,65] including 1 trial (n = 82) conducted in haemodialysis patients and 4 in peritoneal dialysis patients (n = 170). The average residual GFR declined by 1.44 ml/min per 1.73 m^2 in the ACE-inhibitors/ARBs group versus 2.37 ml/min per 1.73 m^2 in the placebo or active control group. The average decline in residual GFR was 0.93 ml/min per 1.73 m^2 (95% CI, 0.38 to 1.47 ml/min per 1.73 m^2) less in patients receiving ACE-inhibitors/ARBs than in placebo or active control group patients ($p < 0.001$) with no evidence of heterogeneity ($I^2 = 0\%$, $p = 0.65$).Three studies including 158 participants reported the changes in urine volume between ACE-inhibitors/ARBs and placebo or active control therapy and found ACE-inhibitors/ARBs treatment was a borderline significant factor in delaying the decline in urine volume: MD 167 ml, 95% CI 21 ml to 357 ml; $p = 0.08$).[66]

In a study by **Ku E *et al*** in 2018 to determine patterns of antihypertensive agent use by stage of CKD and to evaluate the association between different classes of antihypertensive agents with non-renal outcomes, especially in advanced CKD. They studied 3939 participants of the CRIC (Chronic Renal Insufficiency Cohort) study.

Predictors were time-dependent ACE inhibitor or ARB, β-blocker, and calcium channel blocker use (*versus* non-use of agents in each class). Outcomes were adjudicated heart failure events or death. Adjusted Cox models were used to determine the association between predictors and outcomes. They also examined whether the associations differed based on the severity of CKD (early [stage 2-3 CKD] *versus* advanced disease [stage 4-5 CKD]). During median follow-up of 7.5 years, RAAS inhibitor use plateaued during CKD stage 3 (75%) and declined to 37% by stage 5, while β-blocker, calcium channel blocker, and diuretic use increased steadily with advancing CKD. RAAS inhibitor use was associated with lower risk of heart failure (HR, 0.79; 95% confidence interval, 0.67-0.97) and death (HR, 0.78; 95% confidence interval, 0.67-0.90), regardless of severity of CKD. Calcium channel blocker use was not associated with risk of heart failure or death, regardless of the severity of CKD. β-Blocker use was associated with higher risk of heart failure (HR, 1.62; 95% confidence interval, 1.29-2.04) and death (hazard ratio, 1.22; 95% confidence interval, 1.03-1.43), especially during early CKD ($P<0.05$ for interaction). They concluded in their study that ACE inhibitor and ARB use decreased while use of other agents increased with advancing CKD. Use of agents besides angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be associated with suboptimal outcomes in patients with CKD.[67]

In a study conducted by **Qiao Y *et al*** in 2019 to assess the patterns of ACE-Inhibitors/ARBs discontinuation in the setting of CKD progression and identified incident ACE-Inhibitors/ARBs users with a baseline estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2 and without end-stage renal disease in the Geisinger Health System between Jan 1, 2004, and Dec 31, 2015. They investigated the associations of CKD stage, hospitalizations with and without acute kidney injury (AKI), serum potassium, bicarbonate level, thiazide, and loop diuretic use with ACE inhibitors/ARBs discontinuation. It was found that discontinuation of ACE inhibitors/ARBs was common,

particularly in patients with lower eGFR. Hyperkalaemia, hypotension, low bicarbonate level, and hospitalization (AKI-related, in particular) were associated with a higher risk of ACE inhibitors/ARBs discontinuation.[68]

In a study conducted by **Murphy DP *et al*** *in* 2019, they examined ACE inhibitors/ARBs trends from 1999 to 2014 among 38,885 adult National Health and Nutrition Examination Survey participants with creatinine-based eGFR < 60 ml/min per 1.73 m^2 or urinary albumin-to-creatinine ratio ≥ 30 mg/g. Of 7085 participants with CKD, 34.9% used an ACE inhibitors/ARBs. Across four eras studied, rates of use rose significantly (rates were 25.5% in 1999–2002, 33.3% in 2003–2006, 39.0%in 2007–2010, and 40.1% in 2011–2014) but appeared to plateau after 2003 and it was found that in adults with CKD, although use of ACE inhibitors/ARBs increased between 1999 and 2014, it appeared to plateau after 2003, with less than one half of the CKD population using an ACE inhibitors/ARBs.[43]

A study was done on Taiwanese people with CKD, by **Zheng CM *et al,*** in 2019. They included a total of 2,639 patients with CKD and hypertension. They divided the patients into three groups, 217 participants on ACE inhibitor monotherapy, 1,405 on ARBs monotherapy, and 1,017 in the control group. The number of eGFR decline events was 51 (23.5%), 356 (25.3%), and 302(29.7%) for the ACE-inhibitor monotherapy group, the ARBs monotherapy group, and the control group, respectively. When the study group was compared to the control group, the odds ratio, OR was 0.79 with a 95% confidence interval (CI) being 0.67-0.94.In contrast, the adjusted OR was 0.73 (95% CI: 0.54–0.97) when they compared the study group to the control group among patients with CKD stage 3b-5.Consistent with other studies, the number of eGFR decline >5mL/min/1.73m2 or advancement to the dialysis stage events was significantly lower among ACE inhibitor or ARBs users than in the non-user group (29.7% in the non-user group *vs* 25.09% in the user group).[69]

Higuchi S *et al* (2019) evaluated the impact of RAS inhibitors on 2-year all-cause mortality in patients of heart failure with reduced ejection fraction (≤40%) and CKD [(eGFR) <45 mL/min/1.73 m^2] at discharge. They were sub-classified into stages 3B to 5 according to eGFR. They observed that RAS inhibitors were prescribed more frequently in 227 patients with stage 3B than in 107 patients with stage 4 or 5 CKD. All-cause mortality was recorded in 119 patients (55 patients with stage 3B; 64 patients with stage 4 or 5 CKD) during the study period. Based on their findings in these patients, they concluded that RAS inhibitors were associated with reduction in mortality in stage 3B CKD, but the association was less clear in stage 4 or 5 CKD.[70]

Silvariño R *et al* (2019) analyzed the treatment effect of ACE inhibitors, ARBs, and non-ACE inhibitors/ARBs in CKD progression. CKD nondialysis subjects who met the inclusion criteria of at least a 1-year follow-up, 3 clinical visits, and no previous treatment with ACE inhibitor or ARBs were included. From the baseline visit onward, patients were continued with 3 different treatment schemes: no ACE inhibitor/ARBs, started on ACE inhibitors or ARBs, but while avoiding both treatments in combination. The mean age of the subjects was 67.9 ± 15 years and they were followed-up for 3.8 ± 2 years. Estimated glomerular filtration rate averaged 42.1 ± 23 mL/min/1.73 m2 and 300 (27%) patients were found to be diabetics in the study. Progression to ESRD was significantly worse in the no ACE inhibitors/ARBs group versus ACE inhibitors. The analysis showed significantly higher risk of ESRD in the no ACE inhibitors/ARBs group versus ACE inhibitors (p = 0.01). There were no significant differences between ACE inhibitors and ARBs groups regarding the risk of progression to ESRD. Survival was similar in all 3 groups (p = 0.051). A greater number of patients experienced reductions in proteinuria/albuminuria in ACE inhibitors and ARBs groups (together) versus no ACE inhibitors/ARBs group. No difference in hyperkalemia frequency was found between the groups (p = 0.17). It was concluded that in patients with CKD, treatment with ACE inhibitors or ARBs had a superior effect than no ACE inhibitors or

ARBs treatment on slowing kidney disease progression and on proteinuria reduction. Efficacy of ACE inhibitors and ARBs was found to be comparable.[71]

Pecoits-Filho R *et al* in the year 2019 described RAAS inhibitors prescription patterns in the CKD Outcomes and Practice Patterns Study (CKDopps) in Brazil, Germany, France, and the United States (US). 5,870 patients with the mean age 66-72 years were included. Congestive heart failure (CHF) was observed in 11%-19%; diabetes in 43%-54%; serum potassium ≥5 in 20%-35% patients. RAAS inhibitors prescription was more common in Germany (80%) and France (77%) than Brazil (66%) and the United States (52%), where the prevalence of prescription decreased particularly in patients with CKD stage 5. RAAS inhibitors prescription was least common in the United States and more common in patients who were younger, had diabetes, hypertension, or less advanced CKD. They concluded that RAAS inhibitors prescription patterns vary by country and by demographic and clinical characteristics. RAAS inhibitors appeared to be underused, even among patients with strong class-specific recommendations. Although the reasons for this variation could not be fully identified in this cross-sectional observation, their data indicated that the risk of hyperkalemia might contribute to the underuse of this class of agents in moderate to advanced CKD.[72]

A propensity-matched cohort study done by **Arora N *et al*** (2020), included 678 patients in the multicentre Chronic Renal Insufficiency Cohort study. All the patients included in the study had eGFR <30mL/min/1.73m^2. The duration of the study was one year. Mean eGFR of the study group was 25 mL/min/1.73m^2. They had differentiated the patients in four separate groups, *viz-a-viz* always users (reference group) were 386 (57%), never users were 159 (23%), dynamic users were 85 (13%), and new users were 48 (7%). They calculated the relationship between the usage of RAS inhibitors and risk of end stage renal disease. Also, there was no relationship between use of RAS inhibitors and death. Use of RAS inhibitors with

eGFR <30mL/min/1.73m^2 was heterogenous in nature. They concluded that further research is required to identify optimal prescribing strategies for ACE inhibitors in advanced CKD patients.[73]

In a very recent study by **Qiao Y *et al*** in 2020 to investigate the association of ACE inhibitors or ARBs therapy discontinuation after eGFR decreases to below 30 mL/min/1.73 m^2 with the risk of mortality, major adverse cardiovascular events (MACE), and ESKD conducted retrospective, propensity score-matched cohort study included 3909 patients from an integrated health care system that served rural areas of central and north-eastern Pennsylvania. Patients who initiated ACE inhibitors or ARBs therapy from Jan 1, 2004, to Dec 31, 2018, and had an eGFR decrease to below 30 mL/min/1.73 m^2 during therapy were enrolled, with follow-up until Jan 25, 2019. Individuals were classified based on whether they discontinued ACE inhibitors or ARBs therapy within 6 months after an eGFR decrease to below 30 mL/min/1.73 m^2. They found a higher risk of mortality and MACE associated with ACE Inhibitors or ARBs therapy discontinuation after an eGFR decreased below 30 mL/min/1.73 m^2 but no significant difference in the risk of ESKD. Similar patterns held for individuals with a 40% or greater decrease in eGFR. Their findings suggest that continuing ACE Inhibitors or ARBs therapy in patients with declining kidney function may provide cardiovascular and survival benefits without excess risks of ESKD.[74]

In 2020, two researchers, **Zhang Y *et al***, along with their team, did a network meta-analysis of all the randomized clinical trials of patients with stage 3-5 kidney disease. This included relevant studies from MEDLINE and EMBASE, between the years 1950-2018. The patients included in the study were non-dialysis, CKD stage 3-5, treated with RAS inhibitors. There were a total of 44 RCTs with 42,319 patients in the study. CKD 3-5 was defined as GFR <60 mL/min/1.73m^2, and elevated serum creatinine level. In the 33 trials with 23,766 patients, that presented kidney events, they found that treatment with ACE monotherapy was more effective than placebo (OR

0.54, 95% CI 0.41–0.73), control (OR 0.54, 95% CI 0.33–0.87), calcium channel blockers (CCB) (OR 0.67, 95% CI 0.50–0.89), β-blockers (OR 0.60, 95% CI 0.37–0.96) and ARBs (OR 0.71, 95% CI 0.52–0.97). ARBs monotherapy was only better than placebo (OR 0.76, 95% CI 0.58–1.00). Other trials presented cardiovascular events, cardiovascular death, and an all-cause death. 30 studies with 26,144 patients had an all-cause mortality as an outcome. On analysis it was found that intervention with ACE inhibitors the mortality significantly reduced by 23%, 40%, 24%, as compared to placebo, beta blockers, and ARBs.[75]

A study was conducted by **van den Belt SM *et al*** (2020) on 69 children with CKD with mean eGFR <27 ml/min per 1.73 m^2 who discontinued RAAS inhibitors during prospective follow-up. Initial change in BP, albuminuria, and potassium after discontinuation were assessed (median time 6 months). Rate of eGFR decline during a median of 1.9 years before and 1.2 years after discontinuation were estimated. The physician-reported reasons for RAAS inhibitors discontinuation were increase in serum creatinine, hyperkalemia, and symptomatic hypotension. After discontinuation of RAAS inhibitors, BP and albuminuria increased, whereas potassium decreased. eGFR declined more rapidly after discontinuation of RAAS inhibitors (-3.9 ml/min per 1.73 m^2 per year) compared with the slope during RAAS inhibitors treatment (-1.5 ml/min per 1.73 m^2 per year(P=0.005). In contrast, no change in eGFR slope was observed in a matched control cohort of patients in whom RAAS inhibitors was continued. Thus they concluded that the discontinuation of RAAS inhibitors in children with CKD is associated with an acceleration of kidney function decline, even in advanced CKD.[76]

Prasad N *et al* did a longitudinal study of subjects with mild to moderate CKD in 2021 at 11 centres across India. Nearly 3,956 patients, with complete prescription records, were included in the study with a mean age of 50.3 years. The study cohort included 100 (2.5%) patients in stage 1; 309 (7.8%) in stage 2; 3131 (79%) in stage 3, and

426 (10.7%) in stage 4 CKD. The most commonly identified causes of CKD were diabetic kidney disease (24.9%) and chronic interstitial nephritis (23.2%), whereas the cause of CKD could not be determined in approximately 788 (19.4%) participants. Hypertension was the most common comorbidity in nearly 87% of the patients. Nearly 31% of the patients were taking more than 5 different types of drugs, while overall more than half of the patients were taking 5 or more different types of drugs. ACE inhibitors were being used by 22.5% of the patients while ARBs were being used by 25.4% of the patients, making RAAS the most common drug being prescribed for CKD, in their study, 47.9%. Calcium channel blockers were prescribed in 42.6% of patients, diuretics in 28.7%, beta-blockers in 27.1% and alpha-blockers in 10.7% of the patients. It was also seen that the use of ACE inhibitor/ARBs decreased with advancing CKD stages while that of Calcium channel blockers increased.[77]

Loutradis C *et al* (2021) reviewed the use of RAS blockers in patients with advanced CKD. RAS blockers present significant renoprotective effects in CKD patients with very high albuminuria. In post hoc analyses of such trials, these renoprotective effects appeared more robust in patients with more advanced CKD. However, randomized trials specifically addressing whether RAS blockers should be initiated or maintained in patients with advanced CKD are scarce and do not include subjects with normoalbuminuria, thus, many clinicians were unconvinced for the beneficial effects of RAS blockade in these patients. Further, the fear of hyperkalemia or acute renal decline was another factor due to which RAS blockers are usually underprescribed and are easily discontinued in patients with more advanced CKD; i.e., those in Stages 4 and 5.[78]

A study was conducted by **McCoy IE *et al*** (2021) to assess ACE inhibitor and ARBs use among patients with proteinuric CKD and to examine barriers limiting this guideline-concordant care. They observed that only 49% of patients had an active ACE inhibitors/ARBs prescription on the index date, but 87% had been previously prescribed

an ACE inhibitor/ARBs. The use was lower in patients with past AKI, hyperkalemia, CKD stages 4 or 5, and a lack of nephrology care. They concluded that discontinuing, rather than never initiating, ACE inhibitor/ARBs treatment limits guideline-concordant care in proteinuric CKD. Past AKI, hyperkalemia, advanced CKD, and lack of nephrology care were associated with lower use of ACE inhibitors/ARBs, but these putative barriers might be inappropriate in many instances (AKI and advanced CKD) or modifiable (hyperkalemia and lack of nephrology care).[79]

A retrospective cohort study was performed by **Walther CP *et al*** (2021) to investigate the association of ACEI/ARBs discontinuation with outcomes among US veterans with non-dialysis-dependent CKD. They defined the discontinuation events as a gap in ACE inhibitors/ARBs therapy of ≥14 days and subjects were classified further based on duration (14-30, 31-60, 61-90, 91-180 and >180 days). They identified 141,252 people with CKD and incident ACE inhibitors/ARBs use who met the inclusion criteria and followed them for a mean 4.87 years. There were 135,356 discontinuation events, 68,699 deaths and 6,152 incident ESKD events. They concluded that ACE inhibitors/ARBs discontinuation was independently associated with an increased risk of subsequent death and ESKD which may be attributed to the severity of illness factors driving the decision to discontinue therapy.[80]

MATERIALS AND METHODS

Source of Data

This was a prospective observational study done on patients attending OPD, admitted patients from Department of Nephrology and Cardiology during the study duration from Mar 01, 2020 to Feb 28, 2021.

Methods of Collection of Data

INCLUSION CRITERIA:

Patients above the age of 18 years with CKD Stage 3-4 with informed consent were included those having one of the following:

- Patients with Diabetic kidney disease
- Non-Diabetic proteinuric CKD (defined as urine protein excretion greater than 500 mg/day)
- A diagnosis of CHF based on relevant symptoms and signs supported by objective evidence of substantial abnormalities of cardiac function on imaging or invasive hemodynamics.

EXCLUSION CRITERIA:

- Patients who refused to give consent
- Estimated GFR (eGFR) <15 mL/min/1.73m² at baseline
- Patients with age < 18 and > 65 years
- Patients who were pregnant
- Cardiac decompensation requiring inotropic support in the previous 3 months
- Requirement of renal replacement therapy
- A history of primary or severe concomitant valve disease.
- A history of angioedema/cough/allergy previously on use of ACE inhibitors or ARBs
- Serum potassium > 5.5 meq/l at the time of enrolment into the study
- Any contraindication to use of ACE inhibitors or ARBs

A predefined proforma was used to collect the whole data. After an informed consent, relevant history taking, and physical examination was done. Relevant investigations related to the study were done, which included

- Complete Hemogram
- ESR
- Serum creatinine, urea & electrolytes,
- Serum calcium and phosphorus
- Serum alkaline phosphatase
- Uric acid
- Liver function tests
- Urine routine examination
- Spot Urine protein: creatinine ratio
- 24-hour urinary proteins
- USG KUB.
- Chest X ray
- 2D-Echocardiography
- Renal Doppler study

CKD is defined according to the KDIGO practice guidelines [22] as abnormalities of kidney structure or function present for at least 3 months which can be either Markers of kidney damage or low GFR <60 ml/min/1.73m^2. GFR was calculated as per the CKD-EPI equation, as currently recommended by the international consensus KDIGO 2012 guidelines.[22]

Patients of CKD were staged into following categories.

Categories	**GFR (mL/min/1.73 m2)**
G1	≥ 90 Normal or high
G2	60-89 Mildly decreased
G3a	45-59 Mildly to moderately decreased
G3b	30-44 Moderately to severely decreased
G4	15-29 Severely decreased
G5	< 15 Renal failure

Based on the relevant investigations and GFR, those patients found eligible were studied at time of enrolment regarding the baseline parameters, drug history, indications for use of ACE inhibitors / ARBs. If the patient was already taking ACE inhibitors or ARBs before enrolment into the study, information was collected about drug use, duration, dosage, compliance to the treatment and frequency of drug usage. Those patients not taking ACE inhibitors or ARBs but eligible as per the inclusion criteria in the study at the time of enrolment were assessed for their hydration status, additional drug intake like diuretics or NSAIDs. After proper hydration status was confirmed, patients were started on the ACE inhibitors or ARBs on the recommended dosage and frequency. Medication and choice between ACE inhibitors or ARBs were at the discretion of the treating physician with respect to guideline recommended drugs. Target doses and dose equivalents for ACEIs and ARBs were as per recommended guidelines.

Monitoring and Follow Up

Patients were monitored frequently for side effects at regular intervals.

Interval for the further monitoring for side effects with measurements of Blood Pressure, GFR, Serum potassium, 24-hour urinary proteins/ UPCR after initiation of drug or enrolment into the study or after any Change in Dose of Drug follow up was done within 1 week.

Subsequent follow up to monitor the side effects and if dose was stable was done at every 1-2 month with measurements of Blood Pressure, GFR, Serum potassium, 24-houurinary proteins/UPCR, till the completion of follow up at end of 6 months.

Duration Study: Mar 01, 2020 to Feb 28, 2021.

Type of study: Prospective observational study

Outcome Parameters

Outcome of our study was assessed in the form of tolerability of the Patient to the treatment at the end of 6 month follow up.

Outcome status was determined at the follow-up visits and verified either through electronic hospital records or telephone calls to the patients' and their attendants.

STATISTICAL ANALYSIS

Data is being described in terms of frequencies (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations have been done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

The present study was a prospective observational study done on 100 patients with CKD stage 3 & 4 in Department of Nephrology and Cardiology from Mar 01, 2020 to Feb 28, 2021 to study the pattern and outcome of use of ACE inhibitors and ARBs in such patients.

TABLE NO. 1: DISTRIBUTION OF PATIENTS BASED ON USAGE OF ACE INHIBITORS/ARBs AT ENROLMENT

ACE INHIBITORS/ARBs AT ENROLMENT	NO. OF PATIENTS	%AGE
Already taking ACE inhibitors/ARBs at Enrolment	33	33%
New patients started on ACE inhibitors/ARBs	67	67%
Total	100	100%

Out of 100 patients found eligible and those who had given consent for enrolment into the study, 33 patients were already taking ACE inhibitors/ARBs at the time of enrolment whereas remaining 67 patients were not taking any ACE inhibitors/ARBs and they were new patients those were started on ACE inhibitors/ARBs at enrolment in the study.

FIGURE NO. 1: DISTRIBUTION OF PATIENTS BASED ON USAGE ACE INHIBITORS/ARBs AT ENROLMENT

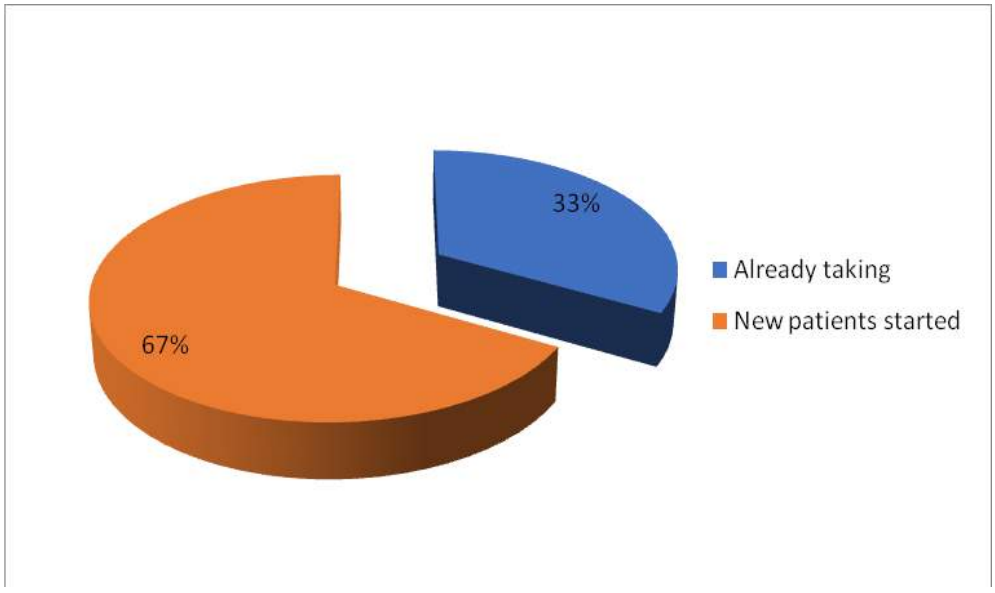


TABLE NO. 2: AGE DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

AGE GROUP (IN YEARS)	NO. OF PATIENTS	%AGE
< 40	3	9%
40-60	18	55%
>60	12	36%
Total	33	100%

Out of 33 patients already taking ACE inhibitors/ARBs at the time of enrolment into the study, majority (55%) were in age group 40-60 years, followed by 36% patients above 60 years of age and remaining 9% were below 40 years of age.

FIGURE NO. 2: AGE DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

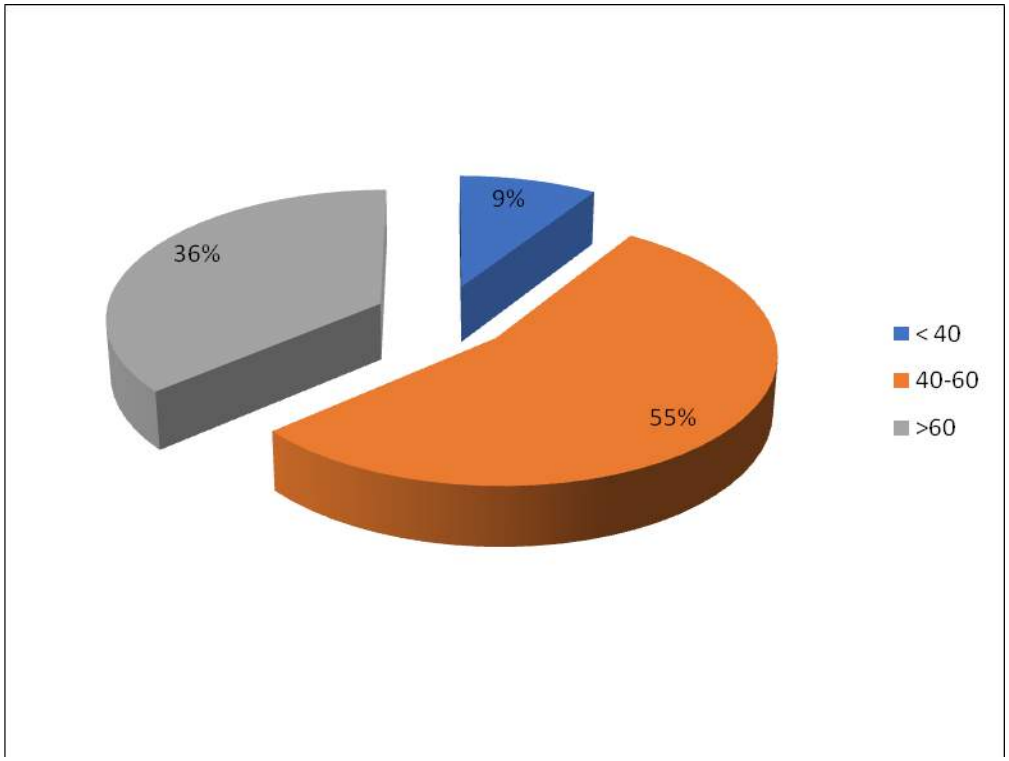


TABLE NO. 3: GENDER DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

SEX	NO. OF PATIENTS	%AGE
MALE	22	67%
FEMALE	11	33%
Total	33	100%

33 patients those who were already taking ACE inhibitors/ARBs at the time of enrolment into the study, consisted of 22 (67%) males and 11 (33%) females.

FIGURE NO. 3: GENDER DISTRIBUTION OF PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

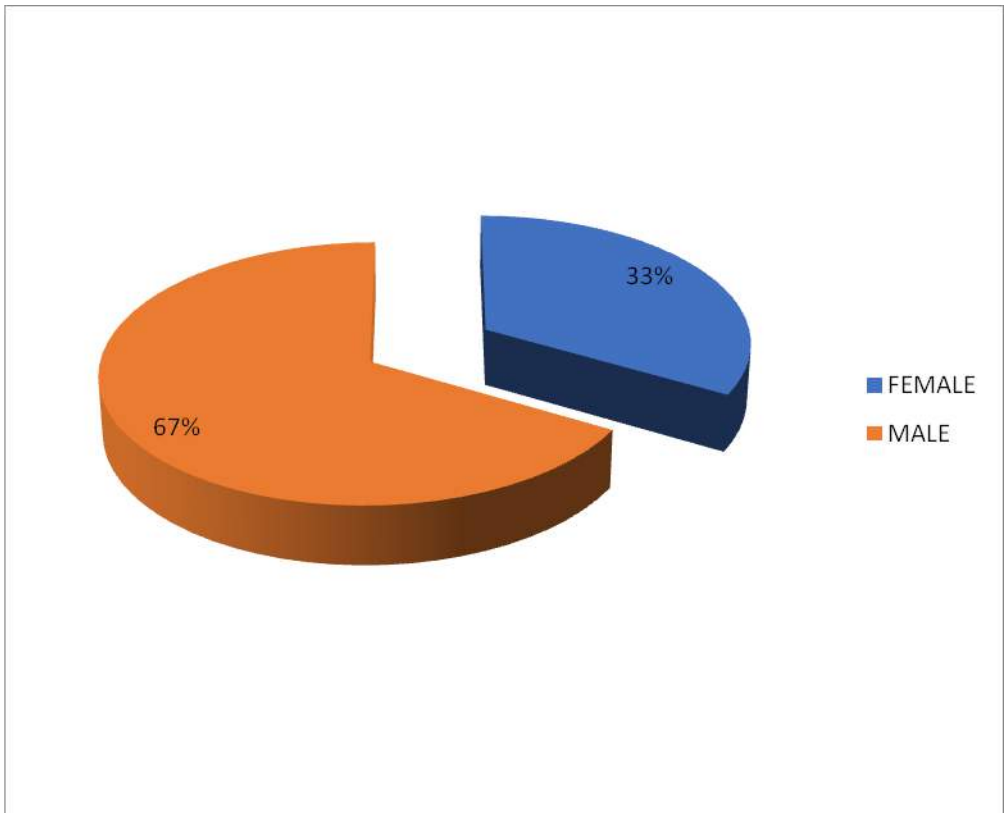


TABLE NO. 4: DISTRIBUTION BASED ON CKD STAGE IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

CKD STAGE	NO. OF PATIENTS	%AGE
3	15	45%
4	18	55%
Total	33	100%

Out of 33 patients already taking ACE inhibitors/ARBs at the time of enrolment, 15 patients i.e. 45% had CKD Stage 3 and 18 patients i.e. 55% had CKD Stage 4.

FIGURE NO. 4: DISTRIBUTION BASED ON CKD STAGE IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

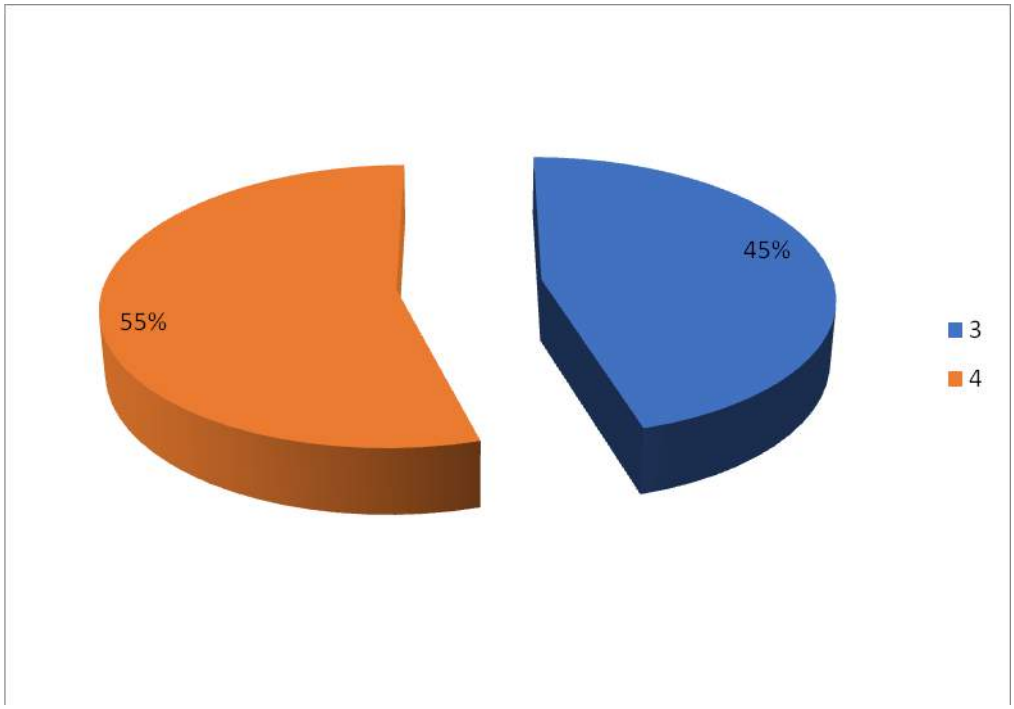


TABLE NO. 5: DISTRIBUTION BASED ON CAUSE OF CKD IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

CAUSE OF CKD	NO. OF PATIENTS	%AGE
DKD	15	45%
GLOMERULAR DISEASE	6	18%
HTN NEPHROSCLEROSIS	3	9%
NOT KNOWN	9	27%
Total	33	100%

Out of 33 patients already taking ACE inhibitors/ARBs at the time of enrolment, on basis of aetiology of CKD, it was observed that 15 patients (45%) had DKD, 6 patients (18%) had glomerular disease, 3 patients (9%) had hypertension (HTN) nephrosclerosis and in remaining 9 patients (27%) aetiology was not known.

Among glomerular aetiology those with records available, out of total 6 patients, 4 were of chronic glomerulonephritis (CGN) and 1 case each of ANCA vasculitis and IgA nephropathy

FIGURE NO. 5: DISTRIBUTION BASED ON CAUSE OF CKD IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

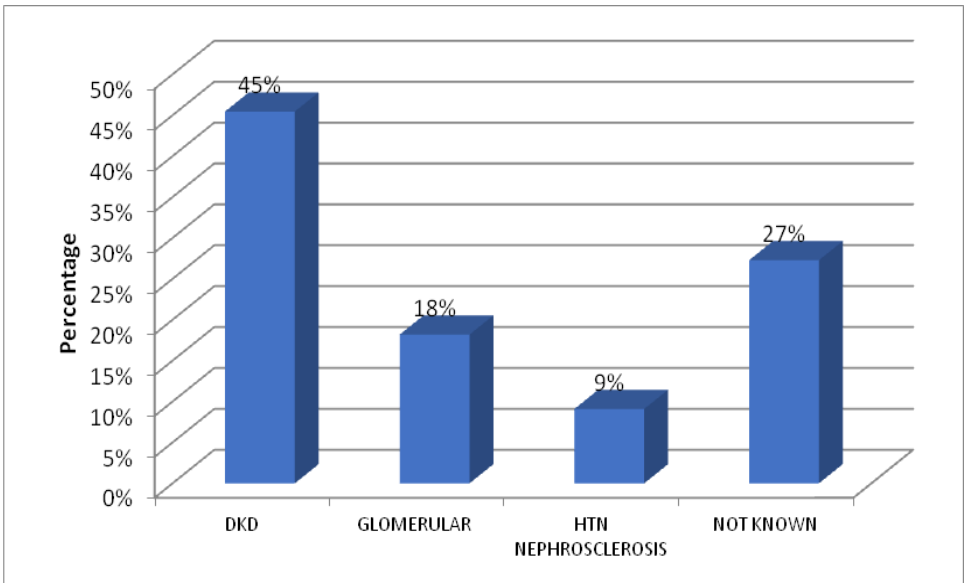


TABLE NO. 6: INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD	NO. OF PATIENTS	%AGE
CHF	6	18%
PROTEINURIC CKD	10	30%
PROTEINURIC CKD+ CHF	17	52%
Total	33	100%

Out of 33 patients already taking ACE Inhibitors/ARBs at enrolment, the indications of treatment with ACE Inhibitors/ARBs in CKD patients were CHF in 6 patients (18%), Proteinuric CKD in 10 patients (30%) and Proteinuric CKD along with CHF in 17 patients (52%).

Among these patients, based on indication of treatment with ACE Inhibitors/ARBS**,** CHF was indication in 23 patients out of which 17 patients had systolic dysfunction, 5 patients had diastolic dysfunction and 1 patient had both systolic and diastolic dysfunction.

FIGURE NO. 6: INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

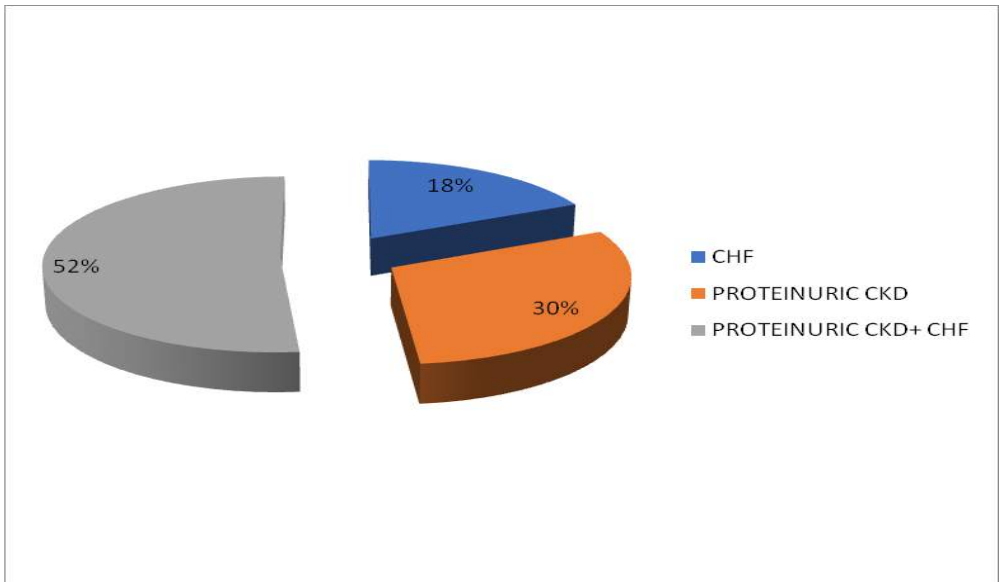


TABLE NO. 7: DISTRIBUTION OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

ACE INHIBITORS/ARBs	NO. OF PATIENTS	%AGE
ACE INHIBITORS	17	52%
ARBs	16	48%
Total	33	100%

FIGURE NO. 7: DISTRIBUTION OF ACE INHIBITORS AND ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

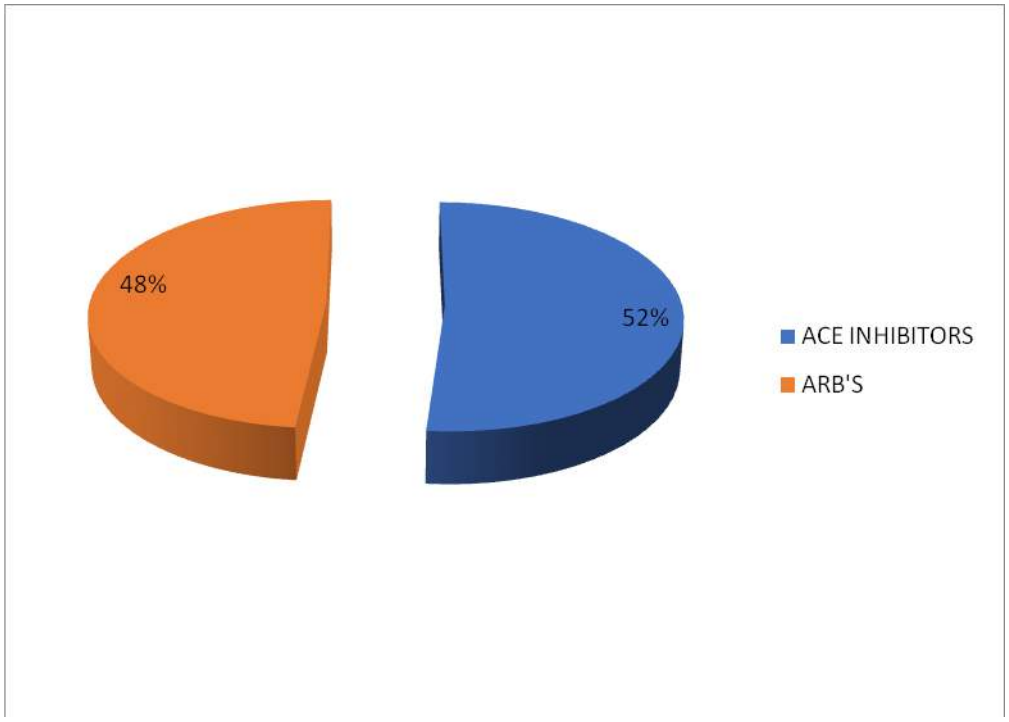


TABLE NO. 8: DISTRIBUTION OF INDIVIDUAL DRUG IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

ACE INHIBITORS/ARBs	NO. OF PATIENTS	%AGE
TELMISARTAN	16	48%
RAMIPRIL	9	28%
ENALAPRIL	8	24%
Total	33	100%

In our study, we observed that out of 33 patients already taking ACE Inhibitors/ARBs at enrolment, 17 patients (52%) were taking ACE Inhibitors whereas 16 patients (48%) were on ARBs. Among the individual drugs, most of patients were taking Telmisartan i.e., 16 patients (48%) followed by Ramipril in 9 patients (28%) and Enalapril in 8 patients (24%).

FIGURE NO. 8: DISTRIBUTION OF INDIVIDUAL DRUG IN PATIENTS ALREADY TAKING ACE INHIBITORS/ARBs AT ENROLMENT

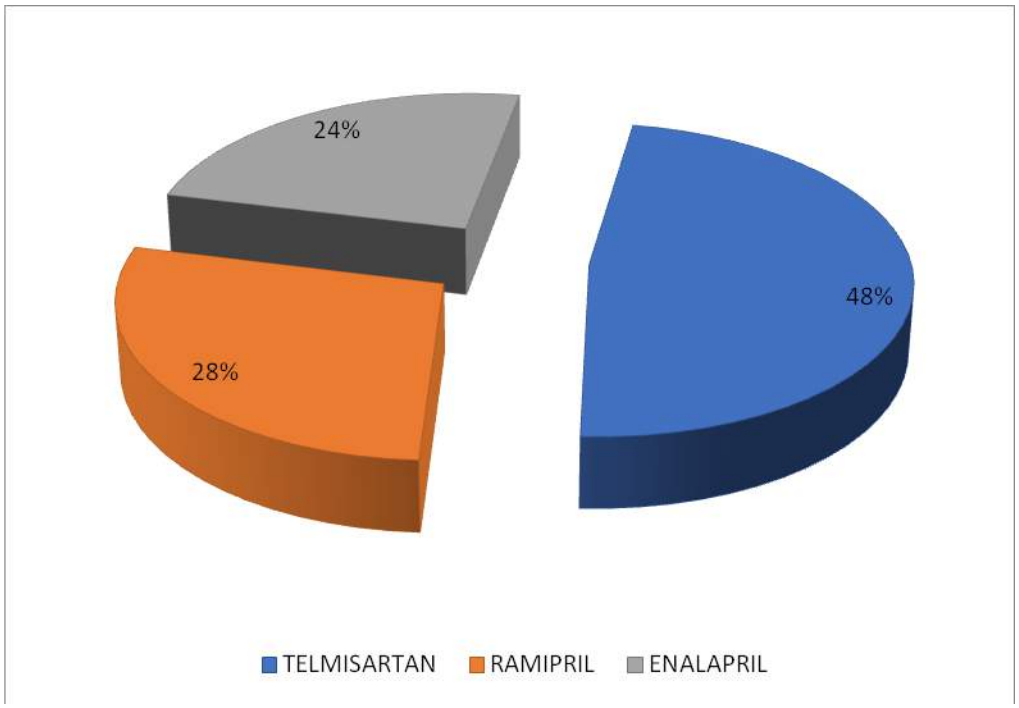


TABLE NO. 9: DURATION OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

DURATION OF PREVIOUS USAGE OF ACE INHIBITORS /ARBs	NO. OF PATIENTS	%AGE
<1 MONTH	3	9%
1-6 MONTHS	19	58%
6-12 MONTHS	10	30%
> 12 MONTHS	1	3%

Out of 33 patients already taking ACE inhibitors/ARBs at enrolment, based on duration of previous usage, 9% patients were taking these for less than 1 month, 58% patients were taking these for the duration of 1-6 months, 30% patients for 6-12 months and only 3% patients were taking for more than 12 months.

FIGURE NO. 9: DURATION OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

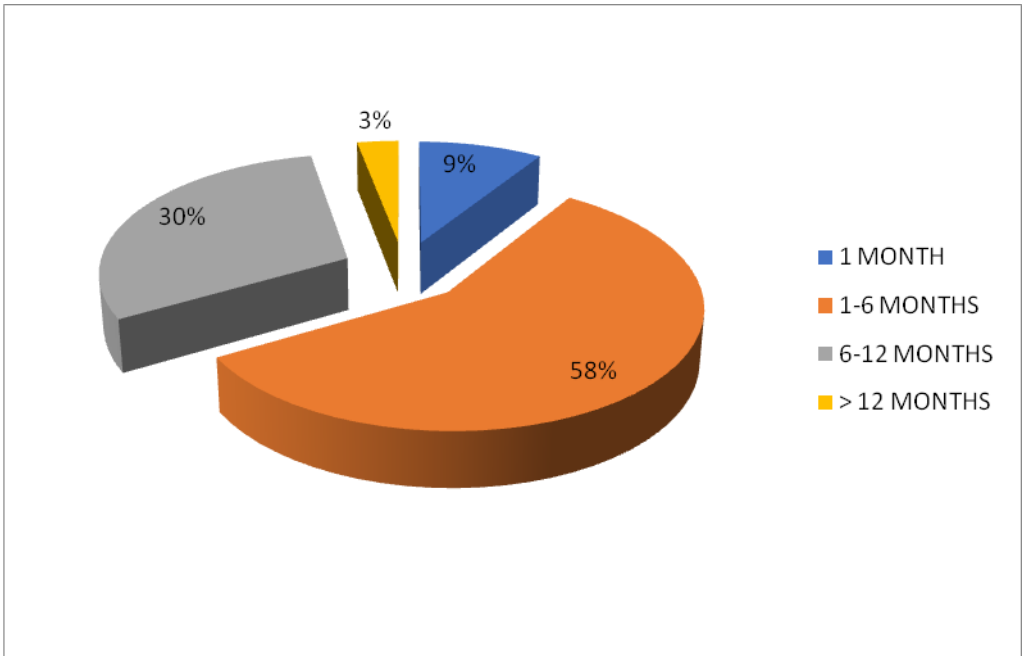


TABLE NO. 10: COMPLICATIONS OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

ANY PREVIOUS COMPLICATION	NO. OF PATIENTS	%AGE
AKI	5	15%
HYPERKALEMIA	4	12%
NONE	24	73%
Total	33	100%

Out of 33 patients already taking ACE inhibitors/ARBs at enrolment, 5 patients (15%) reported with AKI and 4 patients (12%) with hyperkalemia and 24 patients (73%) experienced no previous complications to use of these drugs.

FIGURE NO. 10: COMPLICATIONS OF PREVIOUS USAGE OF ACE INHIBITORS/ARBs IN PATIENTS ALREADY TAKING THESE AT ENROLMENT

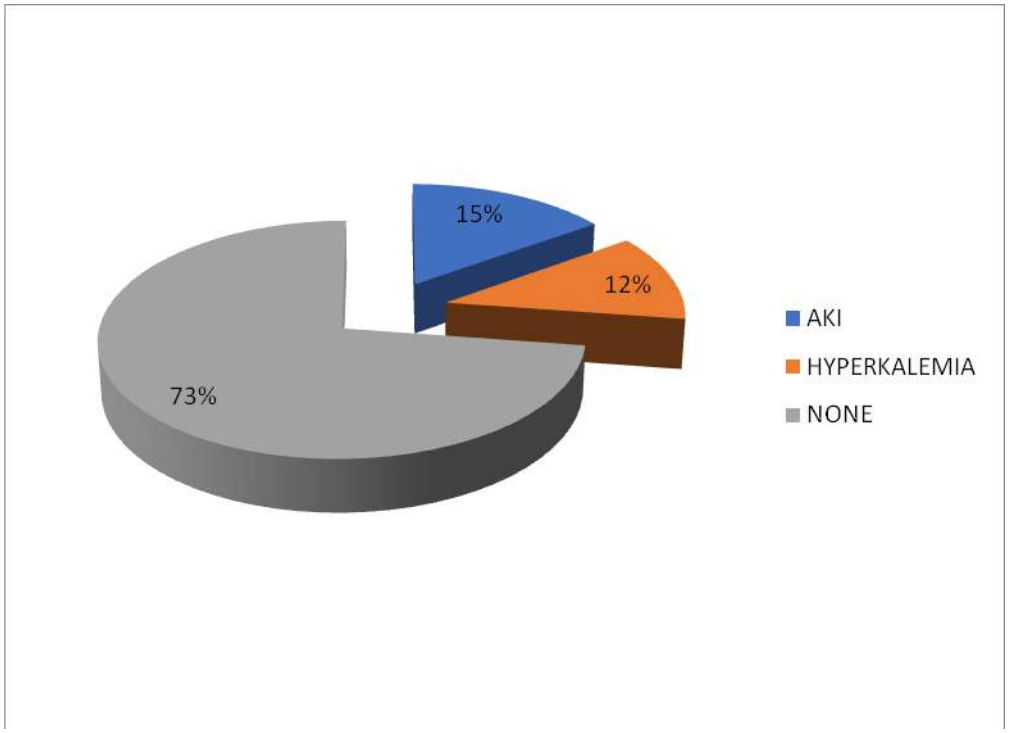


TABLE NO. 11: AGE DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

AGE GROUP (IN YEARS)	NO. OF PATIENTS	%AGE
< 40	9	13%
40-60	35	52%
> 60	23	34%
Total	67	100%

Out of 67 patients those who were not taking ACE Inhibitors/ ARBs at time of enrolment into the study and were started on either of these as per study protocol, maximum patients, 35 patients (52%) were between 40-60 years of age, 23 patients (34%) were above 60 years of age and remaining 9 patients (13%) were less than 40 years of age.

FIGURE NO. 11: AGE DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

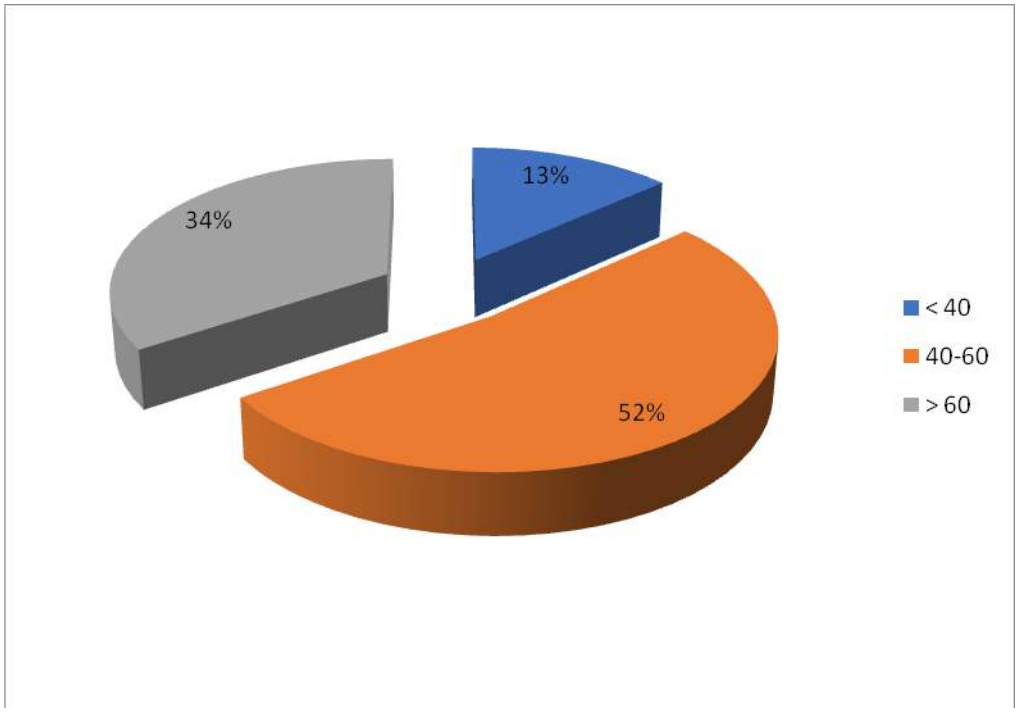


TABLE NO. 12: GENDER DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

SEX	NO. OF PATIENTS	%AGE
MALE	41	61%
FEMALE	26	39%
Total	67	100%

Out of 67 new patients those who were started on ACE Inhibitors/ARBs at time of enrolment, 41 (61%) were males and 26 (39%) were females.

FIGURE NO. 12: GENDER DISTRIBUTION OF NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

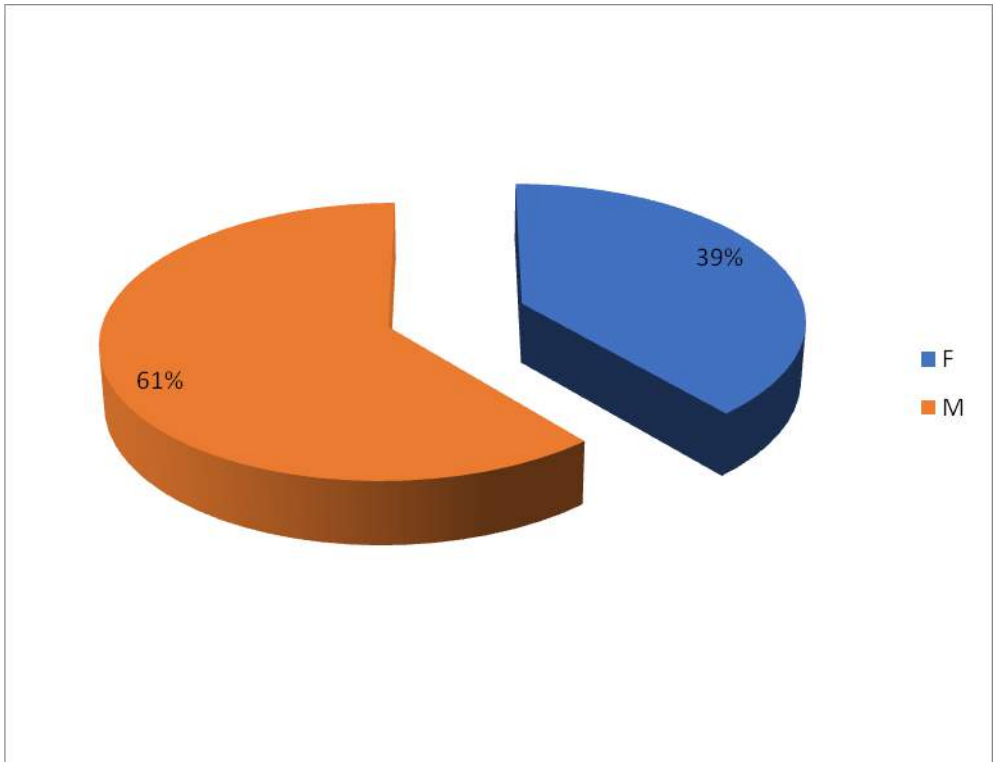


TABLE NO. 13: DISTRIBUTION BASED ON CKD STAGE IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

CKD STAGE	NO. OF PATIENTS	%AGE
3	22	33%
4	45	67%
Total	67	100%

Out of 67 new patients those who were started on ACE Inhibitors/ARBs at time of enrolment, 22 patients i.e. 33 % had CKD Stage 3 and 45 patients i.e. 67% had CKD Stage 4.

FIGURE NO. 13: DISTRIBUTION BASED ON CKD STAGE IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

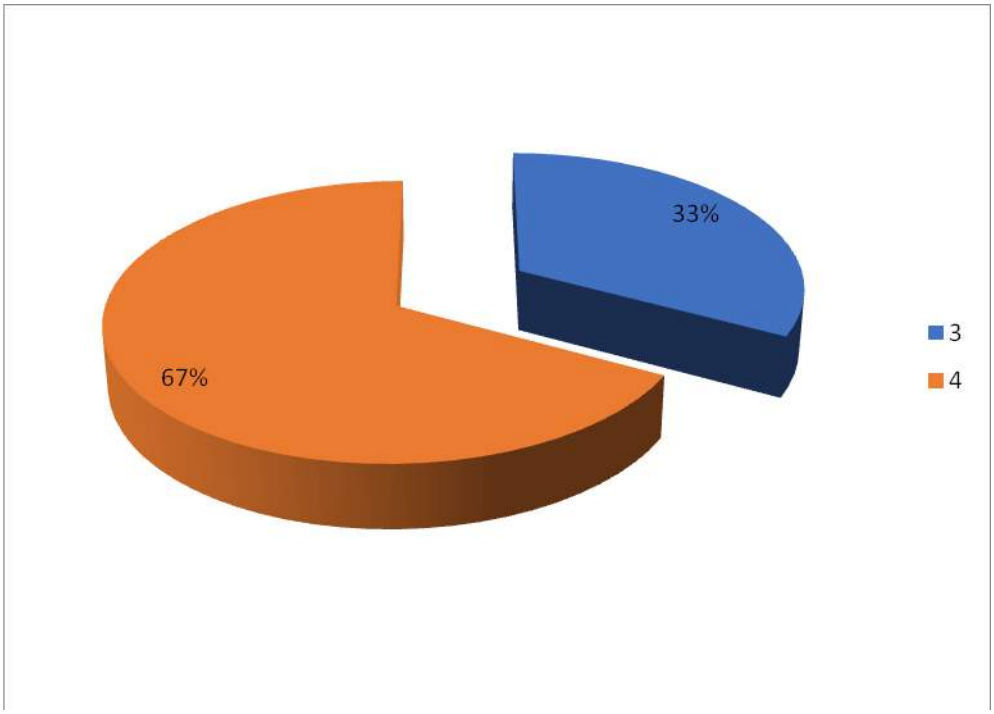


TABLE NO. 14: DISTRIBUTION BASED ON CAUSE OF CKD IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

CAUSE OF CKD	NO. OF PATIENTS	%AGE
DKD	36	54%
HTN NEPHROSCLEROSIS	15	22%
GLOMERULAR CAUSE	3	4%
OTHERS	5	7%
NOT KNOWN	8	12%
Total	67	100%

Out of these 67 patients those who were started on ACE Inhibitors/ ARBs at time of enrolment into the study, based on underlying cause of CKD, 36 patients (54%) were found to have DKD, 15 patients (22%) had HTN nephrosclerosis, 3 patients had glomerular cause (4%) and 5 patients had other causes of CKD and in 8 patients (12%) cause was not clear.

Among the glomerular causes, out of total 3 patients, 2 patients had CGN and FSGS in 1 patient.

Among others, renal calculus disease and chronic pyelonephritis were the cause.

FIGURE NO. 14: DISTRIBUTION BASED ON CAUSE OF CKD IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

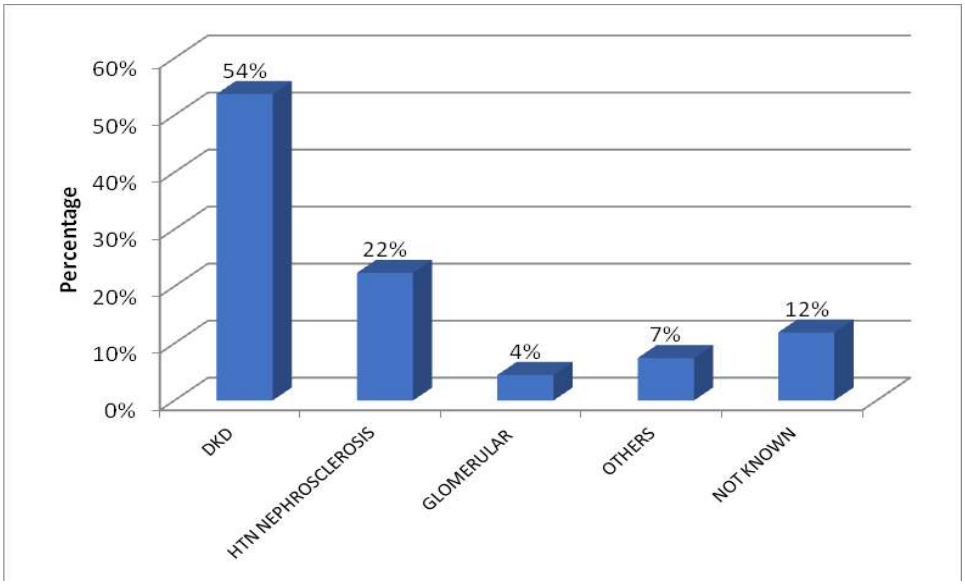


TABLE NO. 15: INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT

INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD	NO. OF PATIENTS	%AGE
PROTEINURIC CKD	54	81%
CHF	5	7%
PROTEINURIC CKD+ CHF	8	12%
Total	67	100%

Out of 67 new patients, those who were started on ACE inhibitors/ARBs at time of enrolment, indications for use of either of these drugs were proteinuric CKD in 54 patients (81%), CHF in 5 patients (7%) and proteinuric CKD along with CHF in 8 patients (12%).

Among the 13 patients with CHF as indication to start with ACE inhibitors/ARBs, systolic dysfunction was present in 8 patients, diastolic dysfunction was present in 4 patients and both systolic and diastolic dysfunction in 1 patient.

FIGURE NO. 15: INDICATIONS OF TREATMENT WITH ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT

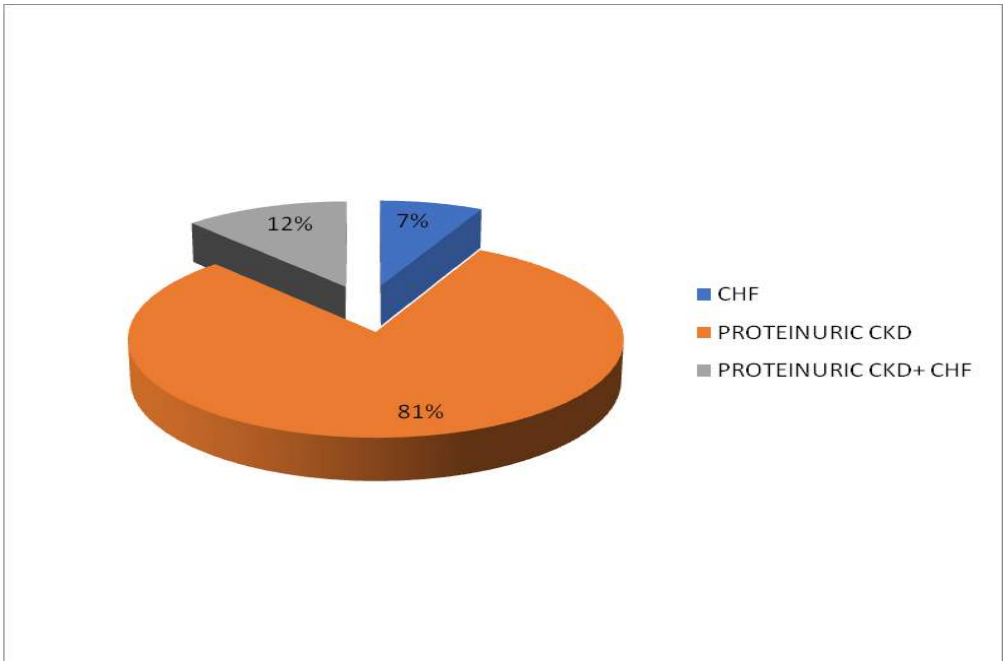


TABLE NO. 16: DISTRIBUTION OF ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT

ACE INHIBITORS/ARBs	NO. OF PATIENTS	%AGE
ARBs	45	67%
ACE INHIBITORS	22	33%
Total	67	100%

FIGURE NO. 16: DISTRIBUTION OF ACE INHIBITORS/ARBs IN NEW PATIENTS STARTED ON THESE AT ENROLMENT

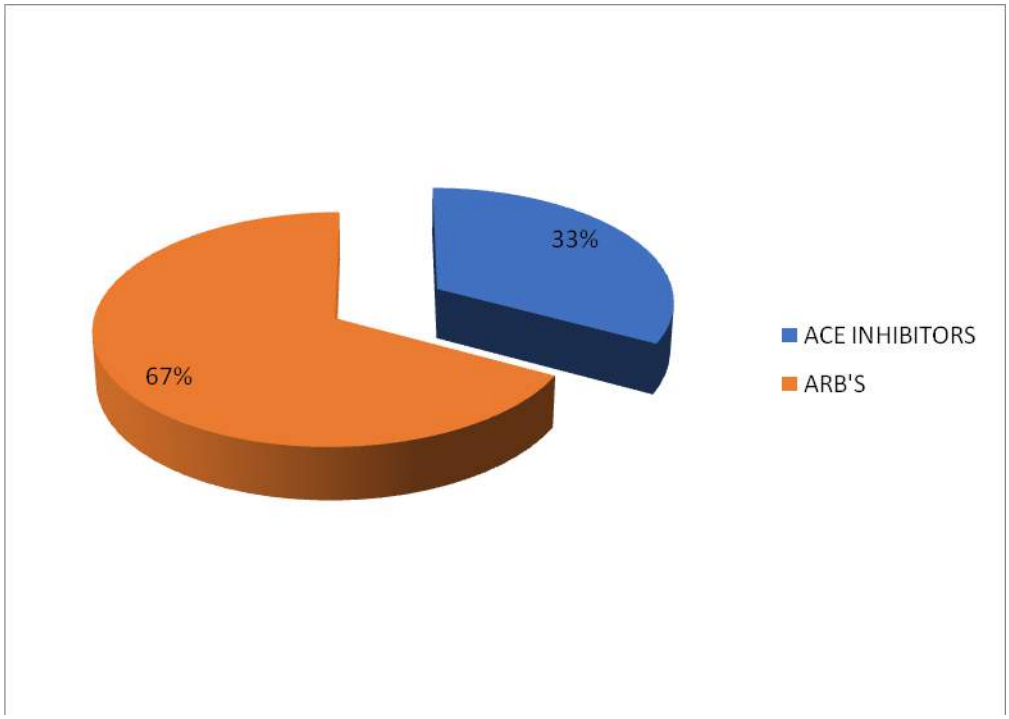


TABLE NO. 17: DISTRIBUTION OF INDIVIDUAL DRUGS IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

ACE INHIBITORS/ARBs PRECSRIBED	NO. OF PATIENTS	%AGE
TELMISARTAN	45	67%
ENALAPRIL	14	21%
RAMIPRIL	8	12%
Total	67	100%

Out of 67 new patients those who were started on ACE inhibitors/ ARBs at time of enrolment, 45 patients (67%) were started on ARBs and 22 patients (33%) were put on ACE Inhibitors for treatment.

Among the individual drugs, Telmisartan was prescribed to 45 patients (67%), Enalapril in 14 patients (21%) and Ramipril was prescribed to 8 new patients (12%).

FIGURE NO. 17: DISTRIBUTION OF INDIVIDUAL DRUGS IN NEW PATIENTS STARTED ON ACE INHIBITORS/ARBs AT ENROLMENT

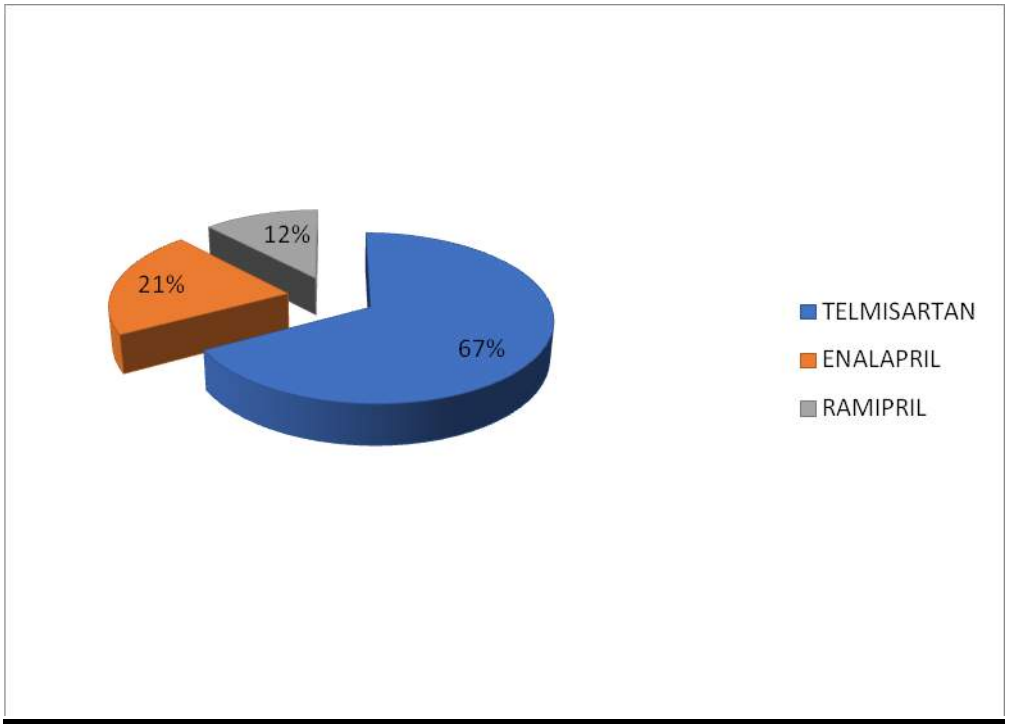


TABLE NO. 18: TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE AFTER ENROLMENT INTO THE STUDY

TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE AFTER ENROLMENT	NO. OF PATIENTS	%AGE
6 MONTHS	62	62%
< 6 MONTHS	38	38%
Total	100	100%

Out of total 100 patients enrolled into the study, 62 patients continued the medication for 6 months of the study period while in 38 patients, the duration of medication intake was less than 6 months after enrolment into the study.

FIGURE NO. 18: TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE AFTER ENROLMENT INTO THE STUDY

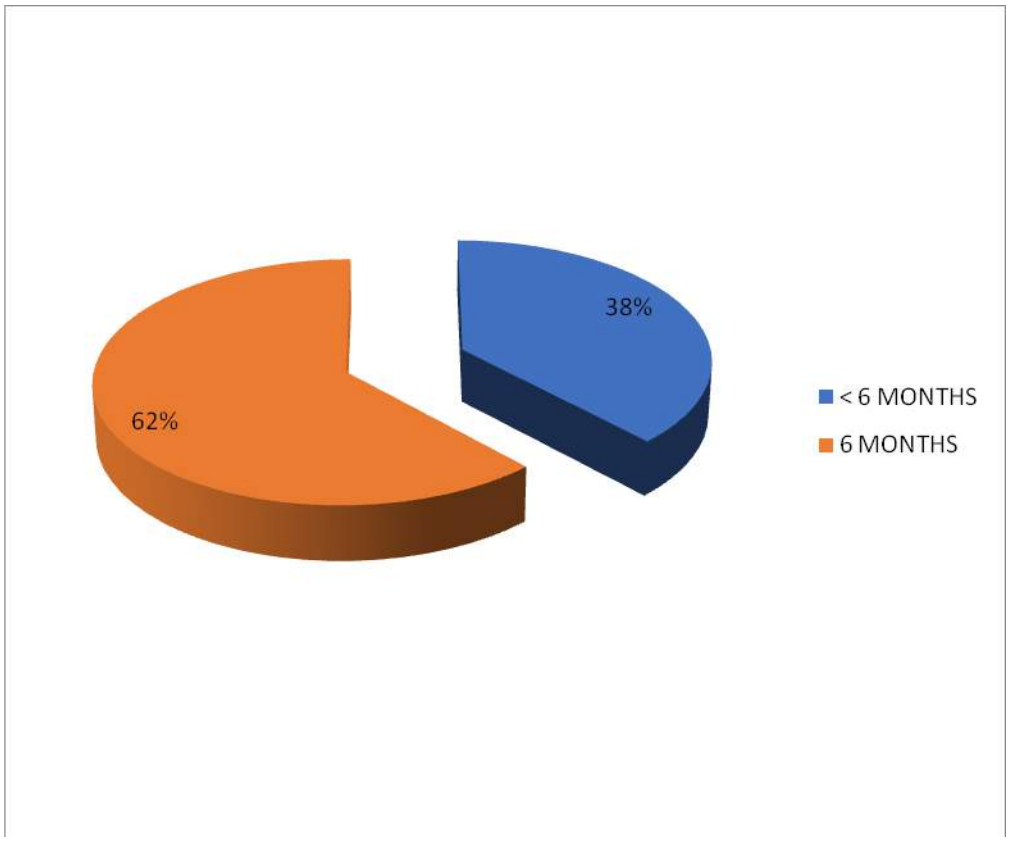


TABLE NO. 19: DISTRIBUTION BASED ON ACE INHIBITORS/ ARBs USE IN THOSE ALREADY TAKING AND NEW PATIENTS STARTED AT ENROLMENT THOSE WHO CONTINUED THEM FOR 6 MONTHS

ACE INHIBITORS/ ARBs AT ENROLMENT	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
Already taking ACE inhibitors/ARBs at Enrolment	33	25	76%
New patients started on ACE inhibitors/ARBs	67	37	55%
Total	100	62	62%

After enrolment into the study, out of 33 patients who were already taking ACE Inhibitors/ARBs at time of enrolment into the study, 25 patients (76%) continued ACE inhibitors/ARBs intake for 6 months. Out of 67 new patients those who were started on ACE inhibitors/ARBs after enrolment into the study, 37 patients (55%) continued the intake for 6 months.

FIGURE NO. 19: DISTRIBUTION BASED ON ACE INHIBITORS/ ARBs USE IN THOSE ALREADY TAKING AND NEW PATIENTS STARTED AT ENROLMENT THOSE WHO CONTINUED THEM FOR 6 MONTHS

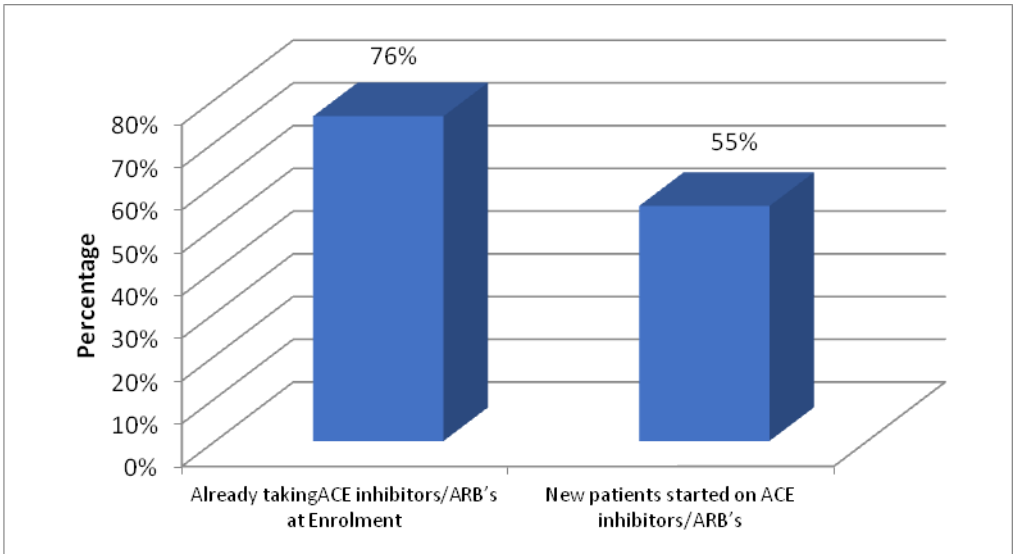


TABLE NO. 20: DISTRIBUTION BASED ON CKD STAGE IN PATIENTS THOSE WHO CONTINUED ACE INHIBITORS/ARBs FOR 6 MONTHS

CKD STAGE	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
3	37	26	70%
4	63	36	57%
Total	100	62	62%

After enrolment into the study, we had total 37 patients of CKD STAGE 3, out of which 26 patients (70%) continued with use of ACE inhibitors/ ARBs for 6 months. There were total 63 patients of CKD Stage 4, out of which 36 patients (57%) continued either of the drug for 6 months.

FIGURE NO. 20: DISTRIBUTION BASED ON CKD STAGE IN PATIENTS THOSE WHO CONTINUED ACE INHIBITORS/ ARBs FOR 6 MONTHS

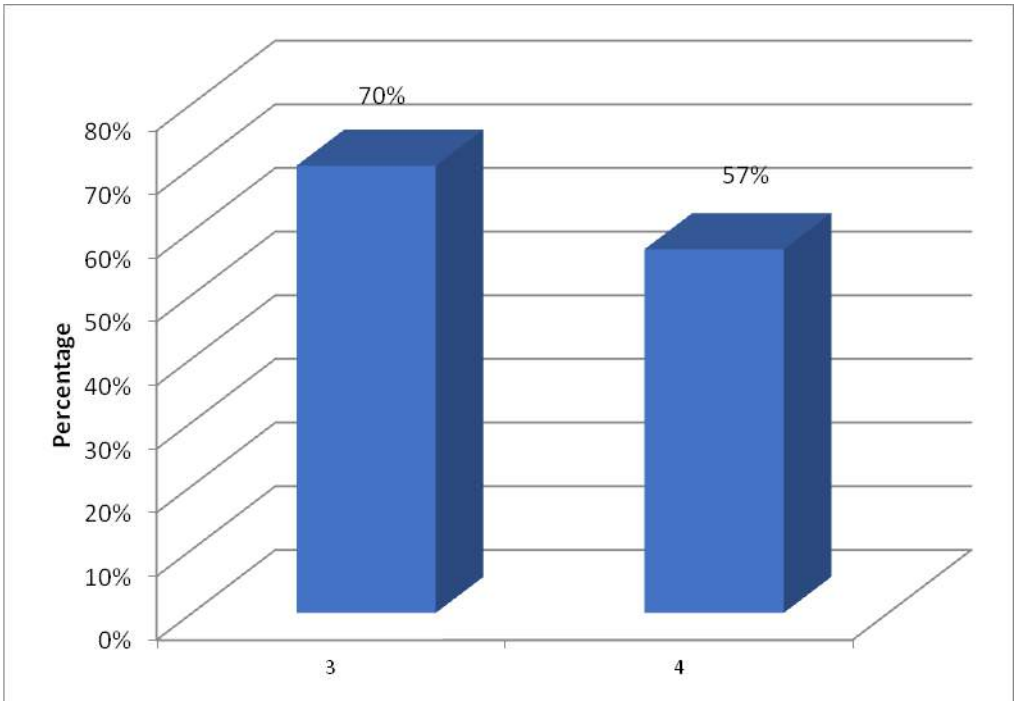


TABLE NO. 21: DISTRIBUTION BASED ON INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
CHF	11	7	64%
PROTEINURIC CKD	64	38	59%
PROTEINURIC CKD+ CHF	25	17	68%
Total	100	62	62%

Out of 100 patients, 62 patients continued the use of ACE Inhibitors/ARBs at the end of 6 months. Based on indication of ACE Inhibitors/ARBs use in CKD, 7 out of 11 patients with CHF (64%), 38 out of 64 patients (59%) with proteinuric CKD, 17 out of 25 patients (68%) with proteinuric CKD along with CHF, continued the use of ACE inhibitors/ARBs for 6 months duration.

FIGURE NO. 21: DISTRIBUTION BASED ON INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

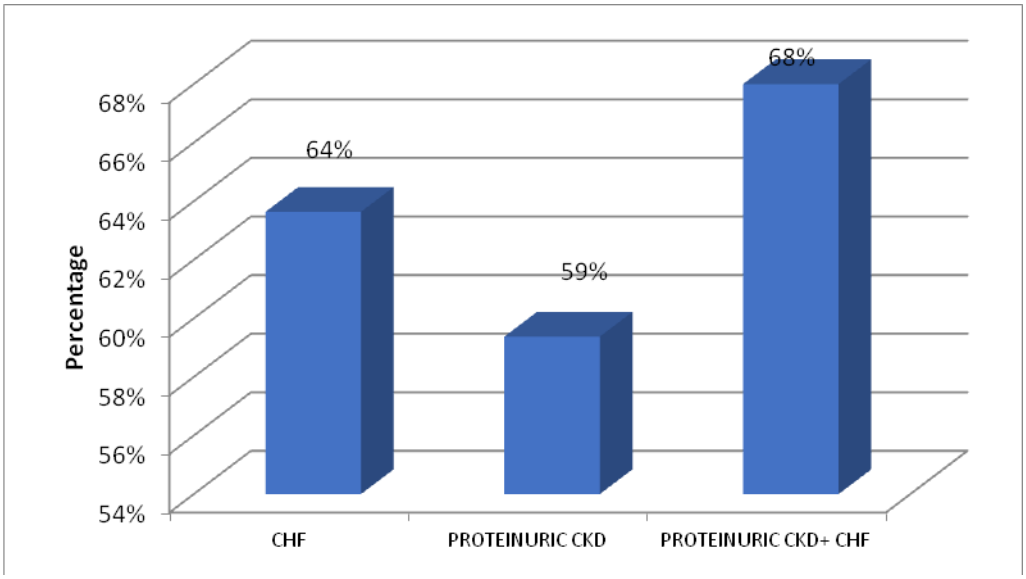


TABLE NO. 22: DISTRIBUTION BASED ON TREATMENT OF CHF WITH ACE INHIBITORS/ARBs IN CKD PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

CHF	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
SYSTOLIC	25	16	64%
DIASTOLIC	9	6	67%
SYSTOLIC+DIASTOLIC	2	2	100%
Total	36	24	67%

24 out of total 36 patients (67%) with CHF who were indicated treatment with ACE inhibitors/ARBs continued the medication intake at the end of 6 months. 16 out of 25 patients (64%) with systolic dysfunction, 6 out of 9 patients (67%) with diastolic dysfunction, and all the patients (100%) with both systolic and diastolic dysfunction continued with ACE inhibitors/ARBs use for 6 months.

FIGURE NO 22: DISTRIBUTION BASED ON TREATMENT OF CHF WITH ACE INHIBITORS/ARBs IN CKD PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

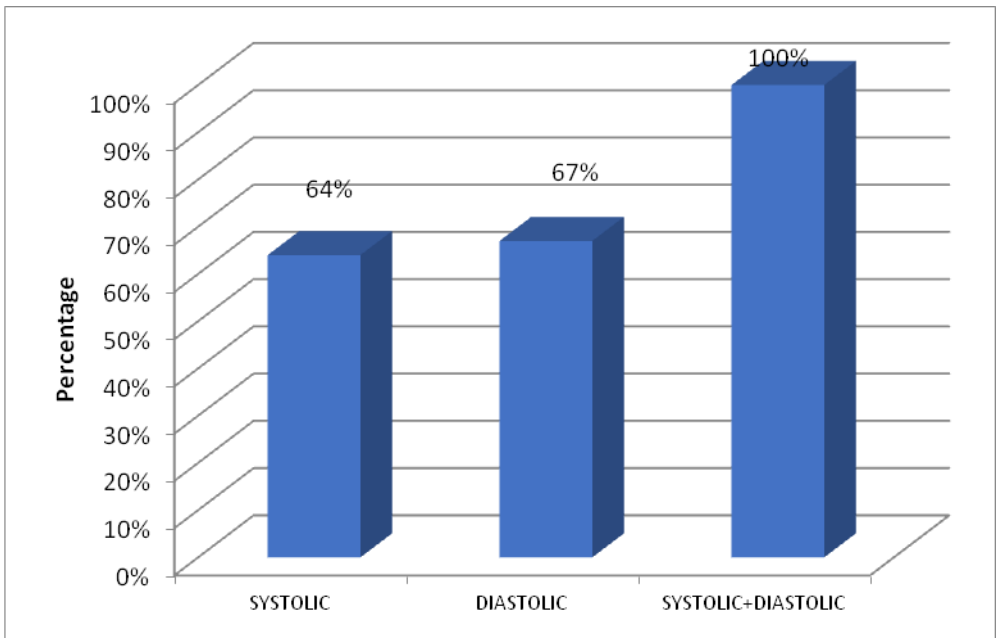


TABLE NO. 23: DISTRIBUTION BASED ON ACE INHIBITORS OR ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

ACE INHIBITORS/ARBs	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
ACE INHIBITORS	39	29	74%
ARBs	61	33	54%
Total	100	62	62%

At the end of 6 months, 62 out of 100 patients who continued the treatment were 74% of patients on ACE Inhibitors (29 out of 39 patients) and 54% of patients on ARBs (33 out of 61 patients).

FIGURE NO. 23: DISTRIBUTION BASED ON ACE INHIBITORS OR ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

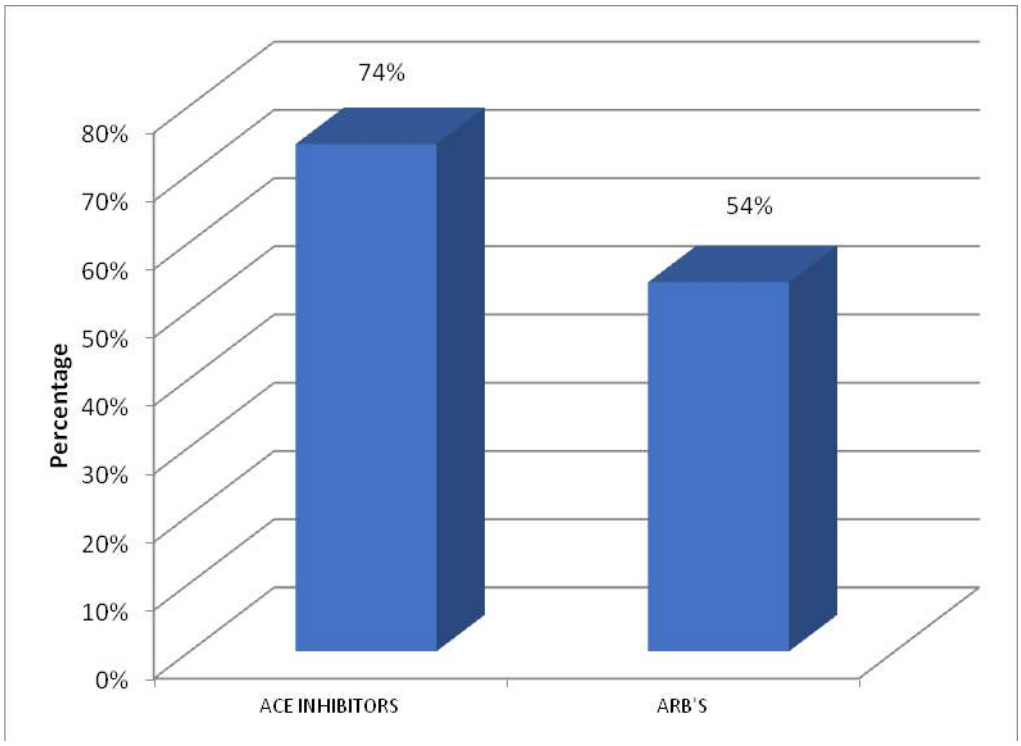


TABLE NO. 24: DISTRIBUTION BASED ON CHANGE IN ACE INHIBITORS/ARBs DOSAGE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

CHANGE IN ACE INHIBITORS/ARBs DOSAGE	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
NO	92	54	59%
YES, INCREASED	8	8	100%
Total	100	62	62%

Out of 100 patients, 92 patients had no change in ACE Inhibitors/ARBs dosage during the course of treatment and only in 8 patients the dosage was increased. 59% of patients (54 out of 92 patients) with no change in dosage and 100% patients with change of dosage continued with either of the drug for 6 months.

FIGURE NO. 24: DISTRIBUTION BASED ON CHANGE IN ACE INHIBITORS/ARBs DOSAGE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

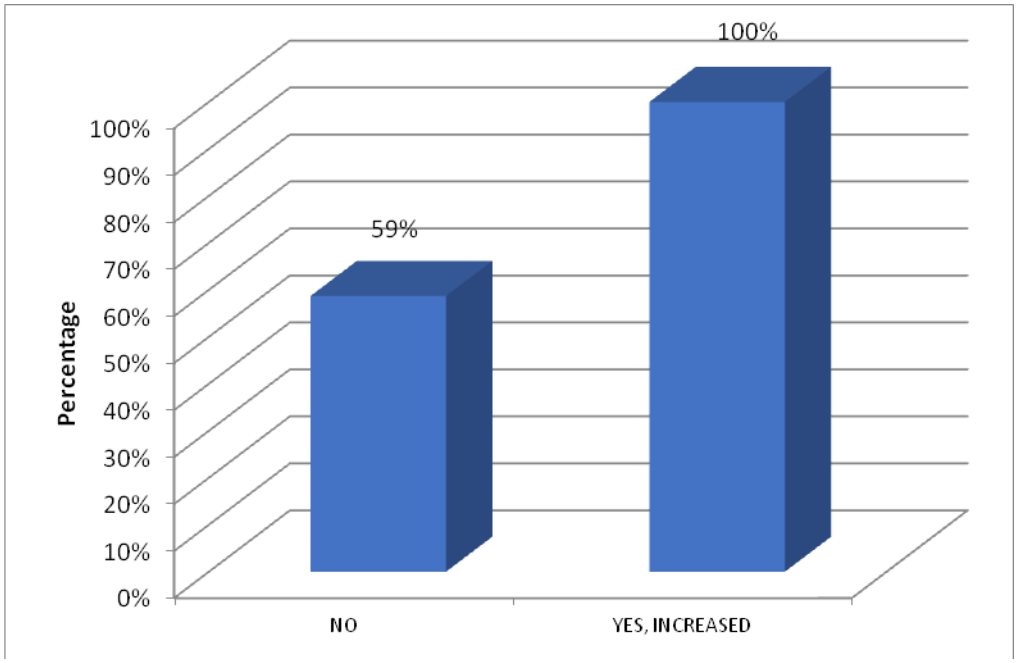


TABLE NO. 25: DISTRIBUTION BASED ON ADVERSE EFFECTS OF ACE INHIBITORS/ARBs IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

ADVERSE EFFECTS	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
		NO. OF PATIENTS	%AGE
HYPERKALEMIA	24	16	67%
AKI	14	5	36%
HYPERKALEMIA+ AKI	15	0	0%
NONE	47	41	87%
Total	100	62	62%

In our study, 24 patients had episodes of hyperkalemia during the study period and 16 out of 24 patients (67%) those with hyperkalemia as adverse effect continued with use of ACE inhibitors/ARBs intake at the end of 6 months.14 patients had AKI as adverse effect while using either of these drugs, 5 out of 14 patients (36%) with AKI continued medication for 6 months. Hyperkalemia along with AKI as an adverse effect was seen in 15 patients. None of these 15 patients were able to tolerate the drug for 6 months and all these patients with hyperkalemia and AKI both discontinued the medication before 6 months before completion of study. 47 patients had no adverse events, out of which 41 patients (87%) continued either of these drug intake for 6 months

FIGURE NO. 25: DISTRIBUTION BASED ON ADVERSE EFFECTS OF ACE INHIBITORS/ARBs IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

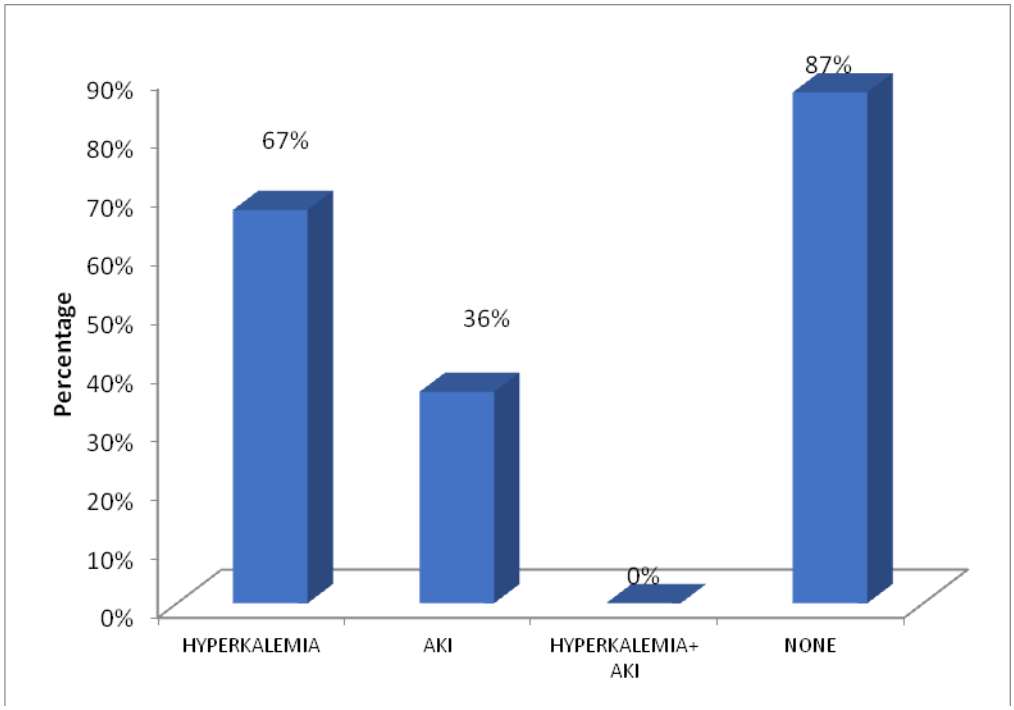


TABLE NO. 26: DISTRIBUTION OF PATIENTS BASED ON EVENT PRECEDING DISCONTINUATION OF ACE INHIBITORS/ARBs WITH DURATION LESS THAN 6 MONTHS

EVENT PRECEDING DISCONTINUATION OF ACE INHIBITORS/ARBs	TOTAL DURATION OF MEDICATION INTAKE < 6 MONTHS	
	NO. OF PATIENTS	%AGE
WORSENING OF GFR	8	8%
HYPERKALEMIA	6	6%
WORSENING OF GFR, HYPERKALEMIA	7	7%
EXPIRED	16	16%
OTHERS	1	1%
Total	38	38%

The events which led to discontinuation of ACE inhibitors/ARBs before 6 months were worsening of GFR in 8 patients, hyperkalemia in 6 patients, worsening of GFR along with hyperkalemia in 7 patients, in 16 patients died during study period and other cause was in 1 case.

FIGURE NO. 26: DISTRIBUTION OF PATIENTS BASED ON EVENT PRECEDING DISCONTINUATION OF ACE INHIBITORS/ARBs WITH DURATION LESS THAN 6 MONTHS

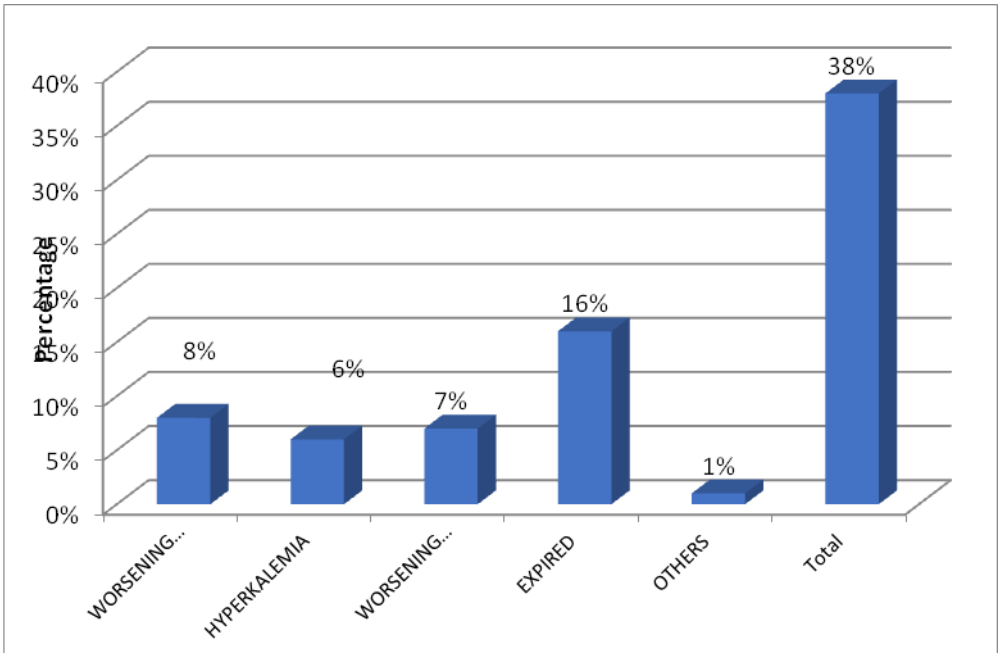


TABLE NO. 27: CHANGE IN CKD STAGING IN THOSE WHO CONTINUED WITH USE OF ACE INHIBITORS/ARBs FOR 6 MONTHS

CKD STAGE	AT ENROLLEMENT	AT END OF 6 MONTH	CHANGE IN CKD STAGING
2	0	3	3
3	26	25	1
4	36	31	5
5	0	3	3
Total	62	62	12

Out of 62 patients those who continued either of the drug for 6 months, 26 patients were in CKD stage 3 and 36 patients were in CKD stage 4 at time of enrolment into the study. We observed that 12 patients out of 62 showed change in CKD staging at the end of 6 months. At the end of 6 months of our study, 25 out of 26 patients with CKD 3 and 31 out 36 patients of CKD 4 had no change in CKD stage. At the end of 6 months, we had 3 patients each with CKD stage 2 and stage 5. Thus, out of total 62 patients those who continued with either of drug for 6 months, 3 patients had improvement in CKD stage while another 3 patients progressed to CKD stage 5.

FIGURE NO. 27: CHANGE IN CKD STAGING IN THOSE WHO CONTINUED WITH USE OF ACE INHIBITORS/ARBs FOR 6 MONTHS

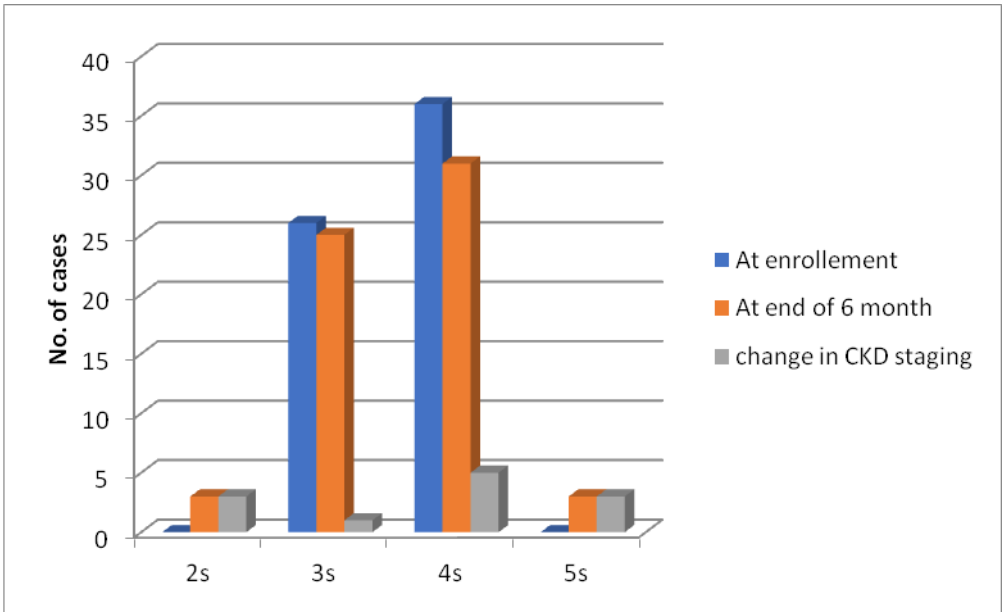


TABLE NO. 28: DISTRIBUTION OF PATIENTS BASED ON CONCOMITANT BETA BLOCKER INTAKE WITH ACE INHIBITORS/ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

USE OF BETA BLOCKERS	TOTAL	TOTAL DURATION OF ACE INHIBITORS/ARBs INTAKE 6 MONTHS	
INDICATION OF TREATMENT WITH ACE INHIBITORS/ARBs IN CKD		NO. OF PATIENTS	%AGE
CHF	8	4	50%
PROTEINURIC CKD	18	16	89%
PROTEINURIC CKD+ CHF	17	13	76%
Total	43	33	77%

43 out of total 100 patients enrolled in the study for ACE Inhibitors/ARBs usage were on concomitant Beta blockers. Based on indication for use of ACE Inhibitors/ARBs in CKD, 8 patients of CHF, 18 patients of Proteinuric CKD and 17 patients with both Proteinuric CKD and CHF were on concomitant Beta blockers use in our study. 4 out of 8 patients (50%) with CHF, 16 out of 18 patients (89%) with Proteinuric CKD and 13 out of 17 patients (76%) with Proteinuric CKD plus CHF both on concomitant beta blockers use continued medication intake for 6 months at the end of study.

FIGURE NO. 28: DISTRIBUTION OF PATIENTS BASED ON CONCOMITANT BETA BLOCKER INTAKE WITH ACE INHIBITORS/ARBs USE IN PATIENTS THOSE WHO CONTINUED THEM FOR 6 MONTHS

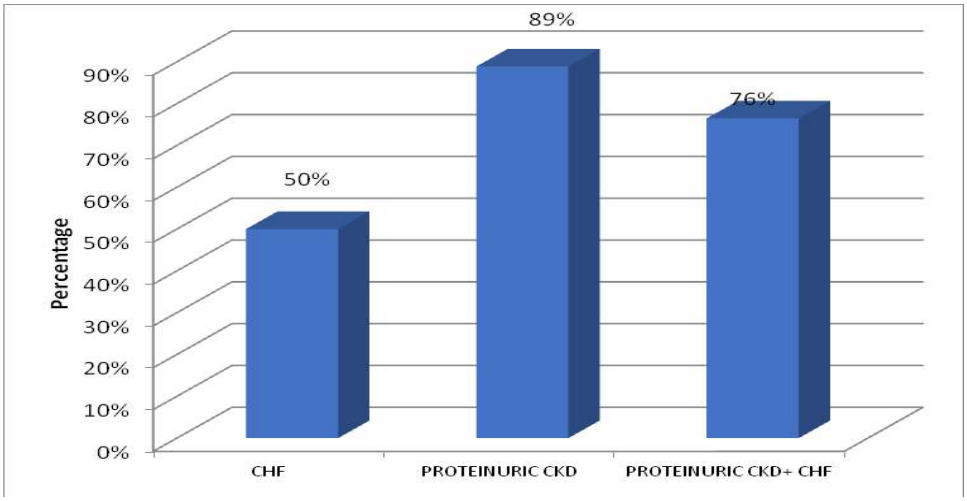


TABLE NO. 29: MORTALITY DATA BASED ON INDICATION OF USE OF ACE INHIBITORS/ARBs IN CKD

INDICATION OF USE OF ACE INHIBITORS/ARBs IN CKD	TOTAL	MORATLITY	
		NO. OF PATIENTS	%AGE
CHF	11	3	27%
PROTEINURIC CKD	64	10	16%
PROTEINURIC CKD+ CHF	25	3	12%
Total	100	16	16%

Based on indication for use of ACE Inhibitors/ARBs in CKD, mortality was observed in 3 out of 11 patients (27%) of CHF, 10 out of 64 patients (16%) of proteinuric CKD and 3 out of 25 patients (12%) of proteinuric CKD plus CHF in our study.

The overall mortality rate was 16%.

FIGURE NO. 29: MORTALITY DATA BASED ON INDICATION OF USE OF ACE INHIBITORS/ARBs IN CKD

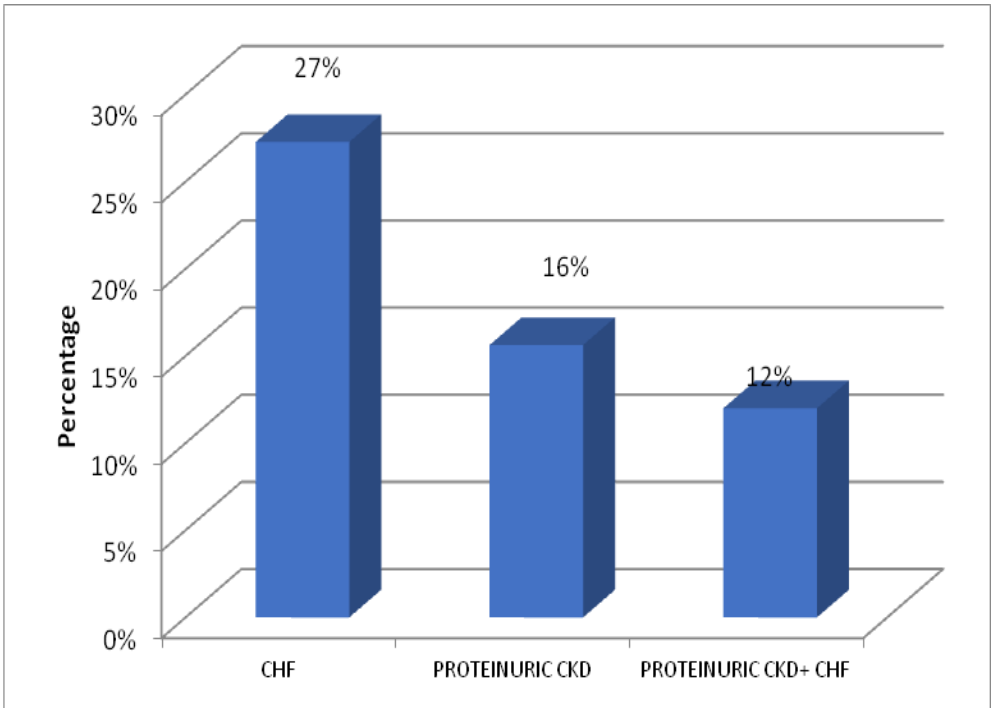
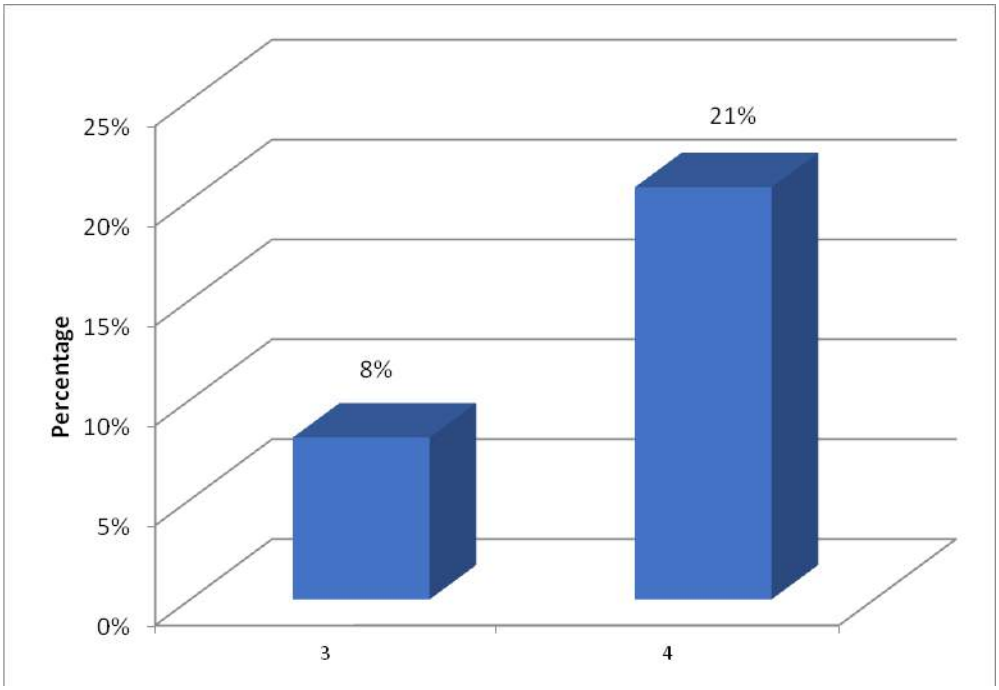


TABLE NO. 30: MORTALITY DATA BASED CKD STAGE AT THE ENROLMENT INTO THE STUDY

CKD STAGE	TOTAL	EXPIRED	
		NO. OF PATIENTS	%AGE
3	37	3	8%
4	63	13	21%
Total	100	16	16%

Based on CKD stage at the enrolment into the study, mortality was observed in 3 out of 37 patients (8% patients) with CKD Stage 3 and 13 out of 63 patients (21% patients) with CKD Stage 4.

FIGURE NO. 30: MORTALITY DATA BASED CKD STAGE AT THE ENROLMENT INTO THE STUDY



DISCUSSION

ACE Inhibitors and ARBs are the best-studied antihypertensive agents that provide significant renal and cardiovascular protection for CKD patients, and have been recommended to be first-line therapy for patients with diabetic and non-diabetic CKD, especially those with proteinuria by KDIGO clinical practice guideline. The guideline also suggests that ACE Inhibitors or ARBs should be preferred therapies in patients with diabetic CKD and proteinuria, even in the absence of high blood pressure.[81] Despite the benefits of ACE inhibitors and ARBs, they may predispose to hyperkalemia and acute kidney injury, risks that are particularly high among patients with low eGFR. Clinical evidence is lacking regarding the risk-benefit balance of discontinuing ACE inhibitors/ARBs in patients with advanced CKD. Recent studies have shown that ACE inhibitor/ARB's use among those with CKD and among CKD-relevant subgroups has declined.[43,77] Hence, the present study was planned to evaluate the pattern and outcome of use of ACE inhibitors and ARB's in CKD stage 3-4 patients.

This study was a prospective observational study done on 100 CKD Stage 3 & 4 patients in the Department of Nephrology and Cardiology. The study population consisted of two groups of patients. We studied both the groups that included patients who were already taking ACE inhibitors/ARB's at the time of enrolment and the new patients those who were prescribed these drugs after enrolment into the study based on the eligibility criteria. This was done to know about the pattern of use of these drugs in CKD stage 3-4 and then we followed both these group of patients for a period of 6 months. This was done to know the outcomes in the form of tolerability of CKD patients to these drugs.

First, out of 100 patients studied in our study, only 33 patients were taking either ACE inhibitors or ARB's already at the time of enrolment and remaining 67 patients were the new patients those who

were started on ACE inhibitors or ARB's as a part of their treatment from the time of their enrolment into the study.

The 33 patients who were already taking ACE inhibitors or ARB's at the time of enrolment consisted predominantly of males (67%) and 33% were females. We found that majority, i.e. 55% of patients were in the age group of 40-60 years. 45% patients had CKD Stage 3 and 55% had Stage 4. Based on etiology of CKD, 45% had DKD, 18% had glomerular disease, 9% had HTN as leading cause of CKD and in remaining 27% etiology was not clear. The indications of treatment with ACE Inhibitors/ARBs in these 33 CKD patients were CHF in 18%, proteinuric CKD in 30% and proteinuric CKD along with CHF in 52%. Thus, the main indication for patients already taking these drugs was proteinuric CKD in maximum number of patients. It was clear from the past records and history of these patients that among the individual drugs, Telmisartan was the most commonly prescribed medication followed by Ramipril and Enalapril.

These 33 patients reported with different durations of usage of these drugs as evident from their previous records and almost all of these were taking drugs for less than 1 year.

Among these patients, as shown from their records and available history, 27% reported with previous complications to use of these drugs and most common complications observed were AKI followed by hyperkalemia in the past which did not lead to discontinuation of the drug among these patients.

It has been seen in various studies that ACE inhibitors and ARBs have been under-prescribed.[67,73,82-84] In the Chronic Renal Insufficiency Study (CRIC) cohort, 70% were receiving RAAS blockers, with as much as 75% and 37% of those in stage 3 and stage 5 CKD, respectively.[67] In the German CKD study, about 83% received RAAS blockers.[85] Similarly, International Network of CKD cohorts documented RAAS blocker use ranged from 54% to 91 %.[86] Proportion of population treated with RAAS blocking agents was quite

variable in Mediterranean countries, reaching up to 39% (Spain, ACE inhibitor only), 62% (France, ACE inhibitor or ARB, 2008), and 53-80% in Italy, 2005.[87,88]

In a recent study on use of ACE inhibitor and ARB's in US from nationally representative data from 1999 to 2014 showed that overall ACE inhibitor/ARBs use during this period was only 34.9% among those with CKD. A significant statement of this study was that the rates of ACE-I/ARBs use increased in the early 2000s among United States adults with CKD, but for unclear reasons, use appeared to plateau in the ensuing decade.[43] In a study done by Arora N *et al*[73] across patients with eGFR < 30 mL/min/1.73 m^2, 23% were not taking an ACE inhibitor/ARBs. In Indian CKD (ICKD) cohort study, Prasad N *et al*[77] noticed only 47% of patients with stage 3 CKD, and 30% of patients with stage 4 CKD were prescribed RAAS blockers.

TABLE 31: PERCENTAGE OF PATIENTS USING ACE INHIBITORS/ARBs IN DIFFERENT STUDIES.

Study	**Percentage of patients using ACE inhibitors/ARBs**
Arora N *et al*[73]	Always users were 57%, dynamic users were 13%, and new users were 7%
Ku E *et al*[67]	75% stage 3; 37% stage 5
Tylicki L *et al*[82]	74%
Winkelmayer WC *et al*[83]	50.7%
Schneider MP *et al*[85]	83%
Alencar de Pinho N *et al*[86]	54 to 91%
Galassi A *et al*[87]	53-80%
Guerin A *et al*[88]	62%
Cheung AK *et al*[89]	59%
Murphy DP *et al*[43]	34.9%
Prasad N *et al*[77]	47.9%

Our study has also verified the same. At the time of enrolment, only 33% of the CKD Stage 3 & 4 patients who had given consent and among reduced footfall in the hospital visit of patients for non-emergency procedures due to COVID-19 restrictions were taking these drugs. It clearly signifies underutilization of these drugs in CKD patients

in our study. Whether this was related to drug preference of physician, fear of complications, more frequent monitoring or poor tolerability to these drugs in more advanced stages of renal failure, we continued to observe these patients for another six months period.

In our study, based on indication for use of these drugs in CKD, CKD patients with cardiac failure already taking these at enrolment were substantially less as compared to proteinuric CKD. Even among patients with proteinuric illnesses, where the indication for their use is the strongest (class I recommendation by KDIGO Blood Pressure Guidelines),[89] only 30 % of patients with proteinuric CKD and 52 % with proteinuric CKD along with cardiac failure were taking these drugs at enrolment in our study. In other study, Pecoits-Filho R *et al* described RAAS inhibitors prescription patterns in the CKD Outcomes and Practice Patterns Study (CKDopps) and found proteinuric CKD with diabetes was present in 43%-54%.[72] In ICKD cohort study by Prasad N *et al*[77] only 59% with proteinuric CKD had been prescribed an ACEI/ARBs and among those 56% had diabetic kidney disease.

Similar to above studies, our study made observation that even with the proteinuric CKD, where the indication for their use is the strongest (class I recommendation by KDIGO Blood Pressure Guidelines),[89] ACE inhibitors/ARBs remain underutilized.

Previous studies by Ahmed A *et al*[90] and another study by Houghton AR *et al*[91] suggest underutilization of ACE inhibitor/ARBs among individuals with congestive heart failure. Another study found that only 17% of heart failure patients were receiving an ACE inhibitor.[92] A similar study in Liverpool found that ACE inhibitors were being prescribed to only 32.7% of heart failure patients.[93] In study by Pecoits-Filho R *et al*, CHF was observed in 11%-19% among RAAS inhibitors prescription patterns in the CKD Outcomes and Practice Patterns Study (CKDopps).[72] The findings in study by Murphy *et al* showed prevalence of ACE-I/ARB's use in the United States adult population with CKD, 57% had indication of cardiac failure.[43] In study

by Arora N *et al*[73], in participants with eGFRs < 30 mL/min/1.73 m^2 43% with diabetes or heart failure were not taking an ACE inhibitor/ARBs.

TABLE 32: PERCENTAGE OF CKD PATIENTS WITH CHF USING ACE INHIBITORS/ARBs IN DIFFERENT STUDIES.

Study	Percentage of CKD patients with CHF using ACE inhibitors/ARBs
Clarke KW *et al*[92]	17%
Mair FS *et al*[93]	32.7%
Pecoits-Filho R *et al*[72]	11-19%
Murphy DP *et al*[43]	57%
Arora N *et al*[73]	43%

Underutilization of ACE inhibitor/ARB may be due to the fear of adverse events such as kidney function deterioration and hypotension, and insufficient appreciation of the benefits of these medications or the prognostic implications of heart failure in CKD.

Respective guidelines for the management of CHF and CKD provide the clinician with a paradox: while renal guidelines recommend not to discontinue ACE inhibitors/ARBs in patients with an eGFR < 30 mL/min/1.73m².[22,94] CHF guidelines advise that ACE inhibitors/ARBs should only be initiated when eGFR is above 30 mL/min/1.73m² and be stopped if it falls below 20 mL/min/1.73m².[95] This may account for the lower utilization of ACE inhibitors/ARBs in clinical practice as eGFR declines.[53,96]

The remaining 67 participants of our study were patients with CKD Stage 3 and 4 those who were prescribed ACE inhibitors or ARBs as per the protocol at the time of enrolment in the study. This group included 61% males and 39% females. Majority of them were in age group between 40-60 years of age. More patients with CKD-4 were started on these drugs. Based on underlying cause of CKD, majority of the patients, 54% were found to have DKD. The indications for use of either of these drugs in these new cases were proteinuric CKD in 81%,

CHF in 7% and proteinuric CKD along with CHF in 12%. Less number of patients with CHF as compared to proteinuric CKD were initiated on treatment. Among the individual drugs, Telmisartan was again most commonly prescribed medication among RAAS blockers followed by Enalapril and then Ramipril.

Both the above group of patients were being followed for a period of 6 months to know the exact duration and factors associated with the tolerability to these drugs.

Out of total 100 patients enrolled into the study, only 62 patients continued the medication for 6 months and rest 38 patients continued the treatment for variable period of time but could not continue the treatment for 6 months at the end of study. 25 patients out of 33 patients (76%) those who were already taking ACE Inhibitors/ARBs at time of enrolment into the study and 37 patients out of 67 new patients (55%) those who were started on ACE inhibitors/ARB's after enrolment into the study, continued the drug intake for 6 months.

Out of total 100 patients, more patients (70%) with CKD Stage 3 continued treatment for 6 months as compared to CKD stage 4 (57%). Based on indication of ACE Inhibitors/ARB use in CKD, 64 % patients with CHF, 59% patients with proteinuric CKD, 68% patients with proteinuric CKD along with CHF, continued the use of ACE inhibitors/ARB's for 6 months duration.

In the present study, patients with cardiac failure those who were indicated treatment with ACE inhibitors/ARBs continued the medication intake at the end of 6 months and no large difference in terms of tolerability was found in those with systolic and diastolic CHF.

In studies done by Ahmed *et al*[57] and other study by Bowling *et al*[97] in CKD patients, Inhibition of the RAS had been shown to be associated with a modest improvement in outcomes in systolic heart failure patients with CKD.[57,97]

In previous studies, these drugs have not been shown to improve outcomes in diastolic heart failure[98-101] taken together with their benefit in systolic heart failure patients with CKD[57], findings of another study by Ahmed A *et al* suggested that ACE inhibitors or ARBs were associated with a significant reduction in all-cause mortality in older patients with diastolic heart failure and CKD, including those with more advanced CKD. Overall evidence suggests that RAS inhibition may be beneficial in heart failure patients with CKD, regardless of ejection fraction.[59] But no data regarding difference in tolerability of these drugs with regard to systolic or diastolic failure is available in above studies.

At the end of 6 months, patients those who continued the treatment were 74% of patients on ACE Inhibitors and 54% of patients were on ARBs.

Bangalore S *et al* in a head-to-head randomized trials found ARBs to be as efficacious and safe as ACE inhibitors, with the added advantage of better tolerability due to lower risk of drug withdrawal due to less adverse effects.[102] Another study by Qaio Y *et al*, among users of ACE inhibitors/ARBs found no difference in risk of discontinuation between people initially prescribed an ACE inhibitors compared to those prescribed an ARBs.[68] In a study by Zhang Y *et al*, it was found that ACE inhibitors were superior to ARBs and other antihypertensive drugs, had the highest probability of being the most beneficial treatments for kidney events, cardiovascular outcomes and all-cause mortality in non-dialysis CKD3–5 patients. In the subgroup of patients with diabetic kidney disease, ARBs were superior to ACE inhibitors in lowering probability of kidney events and cardiovascular events but fell behind ACE inhibitors in all-cause death.[75]

Another study by Xinfang Xie *et al*[103] showed ACE inhibitors reduced risk for all-cause mortality and were superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD.

Today there is more evidence for efficacy of ACE inhibitors, but already many studies have shown ARBs to be equivalent.

In our study, more number of patients on ACE inhibitors continued the treatment for 6 months as compared to ARBs showing better tolerability to ACE inhibitors as compared to ARBs, although greater number of patients were on ARBs (61% on ARBs while 39 % were on ACE inhibitors). However, the data in our study is not sufficient to come to the conclusion whether ACE inhibitors are better or ARBs, in terms of their tolerability and acceptability due to less number of patients and short follow up.

In our study, adverse effects noted to use of ACE inhibitors/ARBs use were hyperkalemia in 24 %, AKI in 14 % and hyperkalemia along with AKI in 15 % and no adverse effect was noted in 47 % patients. 16 out of 24 patients (67%) with hyperkalemia as an adverse effect continued with ACE inhibitors/ARBs intake at the end of 6 months with use of hyperkalemia prevention and management protocols. 5 out of 14 patients (36%) with AKI as an adverse event continued medication for 6 months. None of 15 patients with hyperkalemia and AKI were able to tolerate the drug for 6 months and all these patients discontinued the medication before 6 months or completion of study.

Hyperkalemia is a known complication with RAAS blockade and studies[104-120] have reported increasing incidence of hyperkalemia on use of these drugs in CKD patients. In a study by Readron LC *et al,* hyperkalemia has been reported to occur in up to 10% of outpatients[121] and other study by Ahuja TS *et al* has observed it in up to 38% of hospitalized patients receiving an ACE inhibitor[28].

Hsu TW *et al* in their study found that ACEI/ARBs users (9.2%) had a higher hyperkalaemia-associated hospitalisation rate than non-users (6.7%), but those who developed hyperkalaemia did not significantly have increased risk of pre-dialysis death.[30]

A review of RCTs by Bakris GL *et al* demonstrated a strong association between acute increase of serum creatinine level of up to 30% from baseline that stabilized within 2 months of ACE inhibitor therapy initiation and long-term preservation of kidney function.[122] Another study by Zhang Y *et al*[75] suggested that although RAS blockade therapy definitely increased the likelihood for hyperkalaemia, hypotension, and cough in patients with CKD3–5, it was still more beneficial to protect renal and cardiovascular functions.

In 2018, NKF-KDOQI suggested hyperkalaemia prevention and management protocols, including dietary potassium restriction, correction of acid-base imbalances, avoidance of concomitant use of medications that promote hyperkalaemia, optimisation of diuretic use, and use of cation-exchange resins, may be used to prevent hyperkalaemia when clinically indicated, thus helpful to balance the effects and safety of RAAS blockades.[123]

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD recommended that Continue ACE inhibitor or ARBs therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.[124]

Another recommendation from same guidelines was that hyperkalemia associated with the use of an ACE inhibitors or ARBs can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping the ACE inhibitor or ARBs immediately.[124]

In our study, 67 % patients with hyperkalemia and 36 % AKI alone as an adverse effect were able to continue the treatment at the end of 6 months. Consistent with guidelines and above studies, the utilisation of hyperkalaemia prevention and management protocols helped us to balance serum potassium levels which made it possible to continue the use of RAS inhibition among patients with CKD.

In our study, out of total 100 patients, more patients (70%) with CKD Stage 3 continued treatment for 6 months as compared to CKD stage 4 (57%).

In the present study, events which led to discontinuation of ACE Inhibitors/ARBs before 6 months were worsening of GFR in 8 patients, hyperkalemia in 6 patients, worsening of GFR along with hyperkalemia in 7 patients, death in 16 patients and other cause in 1 case.

In study by Qaio Y *et al*, among users of ACE inhibitors/ARBs, patients with G4 disease (eGFR:15-29 ml/min/1.73 m^2) were more than twice as likely to discontinue therapy compared to people with eGFR ≥ 90 mL/min/1.73m^2.[68]

A meta-analysis showed a pooled discontinuation rate of 6.5% and 4.9% for ACE inhibitor and ARBs users, respectively, over an average of 3.4 years of follow-up.[68,102] Another cohort study of US veterans found discontinuation rates to be high as 34%.[60] Mahmoudpour SH *et al* with a population-based study in the UK found discontinuation rate of 56.8% with ACE inhibitors use at 5 years post-initiation. They also showed that patients who initiated ACE inhibitors/ARBs therapy for renal indications were more likely to discontinue therapy than those who initiated ACE inhibitors/ARBs therapy for other indications. In this study, patients with renal disease and HF patients used ACE inhibitors for the shortest time (average 23.6 and 25.0 months, respectively).[125]

In other study, Molnar MZ *et al* found CKD patients discontinuation rates of ACE inhibitors/ARBs were high and only <10% of patients remained on ACE inhibitors/ARBs therapy throughout all follow-up visits.[60]

Similar to above studies, high discontinuation rate in CKD patients with and without cardiac failure was observed in our study and more patients discontinued the treatment in CKD-4 as compared to CKD-3.

The overall mortality rate in our study was 16%. Patients with CHF had the higher mortality in our study as compared to proteinuric CKD. Further, patients with stage 4 CKD had higher mortality compared to the ones with CKD 3. The real causes of mortality could be a multi factorial determinant in patients with CKD and could not be determined due to the small sample size of our study.

Patients with severe concomitant CKD have been excluded from many trials investigating RAS blockade in CHF. Subgroup analyses of CHF trials and retrospective registry data suggest that ACE inhibitors/ARBs therapy may improve prognosis in patients with CHF and concomitant CKD.[53,57,96,126,127}

Zhang Y *et al* found that intervention with ACE inhibitors, the mortality significantly reduced by 23%, 40%, 24%, as compared to placebo, beta blockers, and ARBs.[75] In another study done by Arora N *et al*,[73] they found no difference in risk for progression to ESRD or mortality across patterns of RAS inhibitor use. Another study on US veterans has found the mortality rate to be 25% in patients receiving RAAS blockers, and 32% in patients not receiving any drugs.[60]

The uncertainty of about the effects of ACE inhibitors and ARBs on the mortality in non-dialysis patients stems for the lack of clinical trials with patient mortality as an endpoint in these population groups. Usually the studies include the renal-end points, and other studies determining the effects of ACE inhibitors or ARBs usually exclude patients with moderate to severe CKD.[128]

Observational studies examining the effect of ACE inhibitors or ARB on mortality in CKD of various stages have yielded inconclusive results, with some showing lower mortality[52,53,129-134] while others showing no change.[96] Molnar MZ *et al* observed 19% lower mortality associated with ACE inhibitors/ARBs administration in intention-to-treat analyses because of such high discontinuation rates.[60]

Several explanations have been proposed for the association between ACE inhibitors/ARBs administration and decreased risk of mortality. ACE inhibitors/ARBs treatment decreases the severity of left ventricular hypertrophy,[135] dilation,[136] remodeling and heart failure[137] commonly seen in CKD, and their treatment could contribute to lower cardiovascular risk. In addition, ACE inhibitors/ARBs are renoprotective in patients with CKD, which could indirectly provide survival benefits.[49,138-140] ACE inhibitors/ARBs administration was associated with a substantially larger survival benefit in diabetic patients compared with non-diabetic patients. Patients with cardiovascular disease, heart failure, and hypertension may overpopulate the diabetic cohort, thus resulting in the larger apparent benefit from ACE inhibitors/ARBs treatment in this subgroup.[60]

The lower mortality associated with RAAS blockers in our study suggests the positive effect of RAAS blockers and calls for more intelligent utilization of these drugs.

The beneficial effects that can lead to better and effective utilization of RAAS blockers can be partly attributed to slower progression of CKD. In our study, we found that only 3 patients out of 62, who were taking RAAS blockers for more than 6 months, had a deterioration of the kidney disease, while 3 patients had an improvement, and the remaining 56 had preserved CKD stage for 6 months. Zheng CM *et al*[66] concluded by their study that ACE inhibitors/ARB treatment retards deterioration of renal function among patients with CKD and hypertension. Higuchi S *et al* found that RAS inhibitors were associated with reduction in mortality in stage 3B CKD, but the association was less clear in stage 4 or 5 CKD.[70] Silvariño R *et al* concluded in their study that in patients with CKD, treatment with ACE inhibitor or ARBs had a superior effect than no ACE inhibitor or ARBs treatment on slowing kidney disease progression and on proteinuria reduction. Efficacy of ACE inhibitor and ARBs were found to be comparable.[71]

It is due to major factor of discontinuance and mortality; we were not able to ascertain the beneficial effects of RAAS blockers in patients with CKD in our limited time period of 6 months and with less number of patients in our study.

43 out of total 100 patients enrolled in the study for ACE Inhibitors/ARBs usage were on concomitant beta-blockers. 33 out of 43 patients (77%) on concomitant beta blockers continued the drug intake for 6 months. Based on indication for use of ACE Inhibitors/ARBs in CKD, 4 out of 8 patients (50%) with CHF, 16 out of 18 patients (89%) with proteinuric CKD and 13 out of 17 patients (76%) with proteinuric CKD plus CHF both on concomitant beta-blockers use continued medication intake for 6 months at the end of study.

Administration of concomitant beta-blockers use was associated with better outcomes for use of ACE inhibitors/ARBs in CKD patients especially those with CHF.

LIMITATIONS

1. A potential limitation of our present study was its observational design. We cannot claim cause and effect but merely describing associations.
2. Certain areas like potential drug-drug interaction, concomitant drug prescriptions and their contribution was needed to be explored further.
3. Data was not captured for drug classes such as sodium-glucose co-transporter 2 inhibitors or glucagon-like peptide 1 receptor agonists, since randomized controlled trials supporting their indications in CKD individuals with renal and cardiovascular end points had been published.
4. The enrolment was very low, partly due to current COVID-19 situation which led to a highly reduced footfall in the hospital for non-emergency procedures.
5. Our study may be confounded by one or many unmeasured covariates.
6. In spite of several limitations like inadequate sample size, study duration, point prevalence nature of the collected data and being uni-centric, this study provided a profile of drug utilization pattern and tolerability in CKD patients compared by CKD staging, drug class and indications of drug. This study will serve as a basis for future comparison.

SUMMARY & CONCLUSION

This study was a prospective observational study done on 100 CKD stage 3 & 4 patients which highlights the pattern and outcome of use of ACE inhibitors and ARBs in CKD 3-4 patients. We observed that-

1. Majority of patients with CKD had diabetes mellitus as the underlying cause of CKD.
2. More number of patients with CKD stage 4 were taking ACE inhibitors/ARBs as compared to patients with CKD stage 3.
3. Telmisartan was the most commonly prescribed RAAS inhibitor in CKD patients.
4. Most common indication for use of these drugs was proteinuric illness as compared to cardiac failure in CKD patients in our study.
5. CKD patients with Cardiac failure and even among patients with proteinuric illnesses, where the indication for their use is the strongest were utilizing these drugs in a substantially less number.
6. Our study reveals the underutilization of these drugs in CKD patients.
7. 62 % CKD patients were able to continue with the use of ACE inhibitors/ARBs for a period of 6 months in our study.
8. Tolerability and acceptability in CKD patients was better as compared to prevalence for use of these drugs in CKD patients.
9. More number of patients on ACE inhibitors continued the treatment for 6 months as compared to ARBs, showing better tolerability to ACE inhibitors as compared to ARBs although more number of patients were on ARBs for treatment.
10. More number of patients with CKD Stage 3 continued treatment for 6 months as compared to CKD stage 4 which signifies less tolerability as the CKD stage advances.
11. In patients with cardiac failure who were indicated treatment with ACE inhibitors/ARB’s, no large difference in terms of tolerability was found in those with systolic and diastolic CHF.

12. Most common adverse effects noted to use of ACE inhibitor/ARBs were hyperkalemia followed by AKI.
13. Utilization of hyperkalemia prevention and management protocols helped us to balance serum potassium levels and made it possible to continue the use of RAS inhibition among patients with CKD.
14. The overall mortality rate in our study was 16%.
15. Patients with CHF had the higher mortality in our study as compared to proteinuric CKD.
16. Patients with CKD stage 4 had higher mortality compared to the ones with CKD stage 3.
17. A prescription for RAAS blockers in patients with CKD was associated with less mortality and in some cases, improvement(s) in kidney function.
18. Administration of concomitant Beta-blockers use was associated with better outcomes for use of ACE inhibitors/ARB's in CKD patients especially those with CHF.
19. It was due to major factor of discontinuance and mortality, our study was not able to ascertain the exact beneficial effects of RAAS blockers in patients with CKD in limited time period of 6 months and less number of patients.
20. Factors associated with underutilization of these drugs in CKD in our study were partly low prescriptions, associated adverse effects leading to discontinuation, high mortality due to underlying disease, progression of disease and in some patients' poor tolerability to these drugs in more advanced stages of renal failure.

Tolerability of patients can be improved by a system of care that ensures regular checks of renal and cardiovascular function. The beneficial effects that can lead to slower progression of CKD can be obtained by regular monitoring and assessment of patients that can lead to better and effective utilization of RAAS blockers. It is, therefore, hoped that this pivotal study will provide new findings to allow future

consideration of a large randomized controlled trial regarding tolerability and outcomes in this important group of patients.

BIBLIOGRAPHY

1. National Kidney Foundation. Global Facts About Kidney Disease. [Internet]. 2017 [cited 2021 Dec 14]. Available from: https://www.kidney.org/kidneydisease/global-facts-about-kidney-disease.
2. Jamison RL. Resolving an 80-yr-old controversy: the beginning of the modern era of renal physiology. AdvPhysiol Educ. 2014;38:286–95.
3. Smith HW. The Kidney. New York: Oxford University Press; 1951.
4. Hall JE. Historical perspective of the renin-angiotensin system. MolBiotechnol. 2003;24:27–39.
5. Gomez RA, Sequeira-Lopez MLS. Renin cells in homeostasis, regeneration and immune defence mechanisms. Nat Rev Nephrol. 2018;14:231-45.
6. Rajagopalan P, Abraham G, Reddy YN, Lakshmanasami R, Prakash ML. Population-based estimation of renal function in healthy young Indian adults based on body mass index and sex correlating renal volume, serum creatinine, and cystatin. Int J NephrolRenovasc Dis. 2016;9:243–7.
7. Abraham G, Varughese S, Thandavan T, Iyengar A, Fernando E, Naqvi SA, *et al*. CKD hotspots in developing countries in South Asia. Clin Kidney J. 2016;9:135–41.
8. ModiGK, Jha V. The incidence of end-stage renal disease in India: a population-based study. Kidney Int. 2006;70:2131–3.
9. Kher V. End-stage renal disease in developing countries. Kidney Int. 2002;26:201–8.
10. Singh AK, Farag YMK, Mittal BV, Reddy SRK, AcharyaVN. Epidemiology and risk factors of CKD in India – results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. 2013;14:14–114.

11. GBD CKD Collaboration. Global, regional, and national burden of CKD, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395:709–33.
12. Levey AS, Atkins R, Coresh J. CKD as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007;72:247–59.
13. Xie X, Liu Y, Perkovic V. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a Bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis. 2016;67:728–41.
14. Dare AJ, Fu SH, Patra J. Renal failure deaths and their risk factors in India 2001-13: nationally representative estimates from the Million Death Study. Lancet Glob Health. 2017;5:e89–95.
15. KDOQI; Clinical Practice Guidelines and Clinical Practice. Recommendations for Anemia in CKD. Am J Kidney Dis. 2006;47:S11-145.
16. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J. Definition and classification of CKD: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney International. 2005;67:2089–100.
17. Varughese S, John GT, Alexander S, Deborah MN, Nithya N, Ahamed I, *et al.* Pre-tertiary hospital care of patients with CKD in India. Indian J Med R. 2007;126:28–33.
18. Varughese S, Abraham G. CKD in India: A Clarion call for change. CJASN. 2018;13:802–4.
19. Moe S, Drueke T, Cunningham J. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69:1945–53.
20. Levin A, Hemmelgarn B, Culletton B. Guidelines for the management of CKD. CMAJ. 2008;179:1154–62.

21. Whelton PK, Carey RM, Aronow WS. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCN A Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2018;71:e127–248.
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of CKD. Kidney Inter Suppl. 2013;3:1–150.
23. American Diabetes Association. Microvascular complications and foot care. Diabetes Care. 2015;38:S58-66.
24. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006;354:131–40.
25. deGoeij MC, Voormolen N, Halbesma N. Association of blood pressure with decline in renal function and time until the start of renal replacement therapy in pre-dialysis patients: a cohort study. BMC Nephrol. 2011;12:38.
26. Rüster C, Wolf G. RAASand progression of renal disease. J Am SocNephrol. 2006;17:2985–91.
27. Tomlinson LA, Abel GA, Chaudhary AN. ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. PLoS One. 2013;8:e78465.
28. Ahuja TS, Freeman D, Mahnken JD, AGraharkar M, Siddiqui M, Memon A. Predictors of the development of hyperkalemia in patients using angiotensin-converting enzyme inhibitors. Am J Nephrol. 2000;20:268–72.
29. Tomson C, Tomlinson LA. Stopping RAS Inhibitors to Minimize Acute Kidney Injury: More Harm than Good? CJASN. 2019;CJN:14021118.

30. Hsu TW, Liu JS, Hung SC. Renoprotective effect of RAAS blockade in patients with predialysis advanced CKD, hypertension, and anemia. JAMA Intern Med. 2014;174:347–54.
31. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? Journal of the American College of Cardiology. 2018;71:1474–82.
32. Pazik J, Ostrowska J, Lewandowski Z, Mróz A, Perkowska-Ptasińska A, Baczkowska T, *et al.* RAAS inhibitors and statins prolong graft survival in post-transplant glomerulonephritis. Ann Transplant. 2008;13:41–5.
33. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990;86:1343–6.
34. Folkow B, Johansson B, Mellander S. The comparative effects of angiotensin and noradrenaline on consecutive vascular sections. Acta Physiol Scand. 1961;53:99–104.
35. Bell L, Madri JA. Influence of the angiotensin system on endothelial and smooth muscle cell migration. Am J Pathol. 1990;137:7–12.
36. Timmermanns PB, Wong PC, Chiu AT, Herblin WF, Benfield P, Carini DJ, *et al.* Angiotensin II receptors and angiotensin II receptor antagonists. Pharmocol Rev. 1993;45:205–51.
37. Heeg JE, de Jong PE, van der Hemm. Reduction of proteinuria by angiotensin converting enzyme inhibition. Kidney Int. 1987;32:78–83.
38. Heeg JE, de Jong P E, van der Hem GK. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. Kidney Int. 1989;36:272–9.
39. Baltatzi M, Savopoulos C, Hatzitolios A. Role of angiotensin converting enzyme inhibitors and angiotensin receptor blockers

in hypertension of CKD and renoprotection. Hihppokratia. 2011;15:27–32.

40. Ahmed A, Jorna T, Bhandari S. Should we STOP angiotensin converting enzyme inhibitors/angiotensin receptor blockers in advanced kidney disease? Nephron. 2016;133:147–8.
41. Bhandari S, Ives N, Brettell EA, Valente M, Cockwell P, Topham PS. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. Nephrol Dial Transplant. 2016;31:255–61.
42. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in CKD. Am J Kidney Dis. 2004;43:S1-290.
43. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use among those with impaired kidney function in the United States. J Am SocNephrol. 2019;30:1314–21.
44. Chen TK, Knicely DH, Grams ME. CKD Diagnosis and Management: A Review. JAMA. 2019;322:1294–304.
45. Inker LA, Astor BC, Fox CH. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63:713–35.
46. Hallan SI, Matsushita K, Sang Y. Age and association of kidney measures with mortality and end-stage renal disease. JAMA. 2012;308:2349–60.
47. Wada T, Haneda M, Furuichi K. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol. 2014;18:613–20.
48. Association AD. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes−2020. Diabetes Care. 2020;43:S135–51.
49. Maschio G, Alberti D, Janin G, Locatelli F, Mann J F, Motolese M. Effect of the angiotensin-converting-enzyme inhibitor

benazepril on the progression of chronic renal insufficiency. N Engl J Med. 1996;334:939–45.

50. Giatras I, Lau J, Levey AS. Effect of Angiotensin-Converting Enzyme Inhibitors on the Progression of Nondiabetic Renal Disease: A Meta-Analysis of Randomized Trials. Ann Intern Med. 1997;127:337–45.
51. Mann J FE, Gerstein H C, Pogue J, Bosch J, Yusuf S. Renal Insufficiency as a Predictor of Cardiovascular Outcomes and the Impact of Ramipril: The HOPE Randomized Trial. Ann Intern Med. 2001;134:629–36.
52. Tokmakova MP, Skali H, Kenchahiah S, Braunwald E, Rouleau JL, Packer M. CKD, Cardiovascular Risk, and Response to Angiotensin-Converting Enzyme Inhibition After Myocardial Infarction - The Survival And Ventricular Enlargement (SAVE) Study. Circulation. 2004;110:3667–73.
53. Berger AK, Duval S, Manske C, Vasquez G, Barber C. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and CKD. Am Heart J. 2007;153:1064–73.
54. Onuigbo MA, Onuigbo NT. Late-onset renal failure from angiotensin blockade (LORFFAB) in 100 CKD patients. IntUrolNephrol. 2008;40:233-9.
55. Kolesnyk I, Strujik DG, Dekker FW, Krediet RT. Effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with CKD. Neth J Med. 2010;68:15–23.
56. Ahmed AK, Kamath NS, Kossi ME, El Nahas AM. The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced CKD. Nephrol Dial Transplant. 2010;25:3977–82.
57. Ahmed A, Fonarow GC, Zhang Y, Sanders PW, Allman RM, Arnett DK, *et al.* Renin-angiotensin inhibition in systolic heart failure and CKD. Epub. 2012;125:399–410.
58. Heywood JT, Fonarow GC, Yancy CW. Comparison of medical therapy dosing in outpatients cared for in cardiology practices

with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. Circ Heart Fail. 2010;3:596–605.

59. Ahmed A, Rich MW, Zile M, Sanders P, Patel K, Zhang Y, *et al.* Renin-Angiotensin Inhibition in Diastolic Heart Failure and CKD. Am J Med. 2012;126:150–61.

60. Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with CKD. J Am Coll Cardiol. 2014;63:650–8.

61. Dattolo PC, Gallo P, Michelassi S, Paudice N, Cannavo R, Romoli E, et al. Conservative management of CKD stage 5: role of angiotensin converting enzyme inhibitors. J Nephrol. 2016;29:809–15.

62. Fröhlich H, Nelges C, Täger T, Schwenger V, Cebola R, Schnorbach J, *et al*. Long-Term Changes of Renal Function in Relation to Ace Inhibitor/ARB Dosing in Patients with Heart Failure and CKD. Am Heart J. 2016;178:28–36.

63. Lin CC, Wu YT, Yang WC, Tsai MJ, Liu JS, Yang CY, *et al.* Angiotensin receptor blockers are associated with lower mortality than ACE inhibitors in predialytic stage 5 CKD: a nationwide study of therapy with renin-angiotensin system blockade. PLoS One. 2017;12:e0189126.

64. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M. Preferred reporting items for systematic review and meta-analysis protocols PRISMA-P 2015 statement. Syst Rev. 2015;4:1.

65. Kjaergaard KD, Peters CD, Jespersen B, Tietze IN, Madsen JK. Angiotensin blockade and progressive loss of kidney function in hemodialysis patients: a randomized controlled trial. Am J Kidney Dis. 2014;64:892–901.

66. Liu Y, Ma X, Zheng J, Jia J, Yan T. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and residual renal function in dialysis

patients: a meta-analysis of randomised controlled trials. BMC Nephrol. 2017;18:206.

67. Ku E, McCulloch CE, Vittinghoff E, Lin F, Johansen KL. Use of antihypertensive agents and association with risk of adverse outcomes in CKD: focus on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. J Am Heart Assoc. 2018;7:e009992.
68. Qiao Y, Shin JI, Sang Y, Inker LA, Secora A, Coresh J, *et al.* Discontinuation of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in CKD. Mayo Clinic Proc. 2019;94:2220–9.
69. Zheng CM, Wang JY, Chen TT, Wu Y-C, Wu Y-L. Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker monotherapy retard deterioration of renal function in Taiwanese CKD population. Scientific Reports. 2019;9:2694.
70. Higuchi S, Kohsaka S, Shiraishi Y, Katsuki T, Nagatomo Y, Mizuno A, *et al.* Association of renin-angiotensin system inhibitors with long-term outcomes in patients with systolic heart failure and moderate-to-severe kidney function impairment. Eur J Intern Med. 2019;62:58-66.
71. Silvariño R, Rios P, Baldovinos G, Chichet MA, Perg N, Sola L, *et al.* Is CKD Progression Influenced by the Type of Renin-Angiotensin-System Blocker Used? Nephron. 2019;143:100-7.
72. Pecoits-Filho R, Fliser D, Tu C, Zee J, Bieber B, Wong MMY*, et al.* Prescription of RAAS inhibitors (RAASi) and its determinants in patients with advanced CKD under nephrologist care. J Clin Hypertens (Greenwich). 2019;21:991-1001.
73. Arora N, Katz R, Bansal N. ACE Inhibitor/Angiotensin Receptor Blocker Use Patterns in Advanced CKD and Risk of Kidney Failure and Death. Kidney Med. 2020;2:248–57.
74. Qiao Y, Shin J, Chen TK. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. JAMA Intern Med. 2020;180:718–26.

75. Zhang Y, Dandan H, Zhang W, Xing Y, Guo Y. ACE Inhibitor Benefit to Kidney and Cardiovascular Outcomes for Patients with Non-Dialysis CKD Stages 3–5: A Network Meta-Analysis of Randomised Clinical Trials. Drugs. 2020;80:797–811.
76. van den Belt SM, Heerspink HJL, Kirchner M, Gracchi V, Thurn-Valsassina D, Bayazit AK, *et al* . Discontinuation of RAAS Inhibition in Children with Advanced CKD. Clin J Am SocNephrol. 2020;15:625-32.
77. Prasad N, Yadav AK, Kundu M, Sethi J, Jaryal A. Prescription Practices in Patients With Mild to Moderate CKD in India. Kidney Int Rep. 2021;6:2455–62.
78. Loutradis C, Price A, Ferro CJ, Sarafidis P. Renin-angiotensin system blockade in patients with CKD: benefits, problems in everyday clinical use, and open questions for advanced renal dysfunction. J Hum Hypertens. 2021;35:499-509.
79. McCoy IE, Han J, Montez-Rath ME, Chertow GM. Barriers to ACEI/ARB Use in Proteinuric CKD: An Observational Study. Mayo Clin Proc. 2021;96:2114-22.
80. Walther CP, Winkelmayer WC, Richardson PA, Virani SS, Navaneethan SD. Renin-angiotensin system blocker discontinuation and adverse outcomes in CKD. Nephrol Dial Transplant. 2021;36:1893-9.
81. Taler SJ, Agarwal R, Bakris GL, Flynn JT, Nilsson PM, Rahman M, *et al*. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. Am J Kidney Dis. 2013;62:201-13.
82. Tylicki L, Jakubowska A, Lizakowski S, Swietlik D, Rutkowski B. Management of renin-angiotensin system blockade in patients with CKD under specialist care. Retrospective cross-sectional study. J Renin Angiotensin Aldosterone Syst. 2015;16:145-52.
83. Winkelmayer WC, Fischer MA, Schneeweiss S, Wang PS, Levin R, Avorn J. Underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. Am J Kidney Dis. 2005;46:1080-7.

84. Pappoe LS, Winkelmayer WC. ACE inhibitor and angiotensin II type 1 receptor antagonist therapies in elderly patients with diabetes mellitus: are they underutilized? Drugs Aging. 2010;27:87-94.
85. Schneider MP, Hilgers KF, Schmid M, Hübner S, Nadal J, Seitz D, *et al.* Correction: Blood pressure control in CKD: A cross-sectional analysis from the German CKD (GCKD) study. PLoS One. 2018;13:e0204340.
86. Alencar de Pinho N, Levin A, Fukagawa M, Hoy WE, Pecoits-Filho R, Reichel H, *et al.* Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in CKD. Kidney Int. 2019;96:983-94.
87. Galassi A, Brancaccio D, Cozzolino M. Awareness of hypertension and proteinuria in randomly selected patients in 11 Italian cities. A 2005 report of the National Kidney Foundation of Italy. J Clin Hypertens (Greenwich). 2009;11:138–43.
88. Guerin A, Maumus-Robert S, Zin A. Insufficient therapeutic management of hypertensive patients with renal failure in France. Arch Cardiovasc Dis. 2008;101:705–13.
89. Cheung AK, Chang TI, Cushman WC. Blood pressure in CKD: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95:1027–36.
90. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? J Am Geriatr Soc. 2002;50:1297-1300.
91. Houghton AR, Cowley AJ. Why are angiotensin converting enzyme inhibitors underutilised in the treatment of heart failure by general practitioners? International Journal of Cardiology. 1997;59:7-10.
92. Clarke KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. Br Heart J. 1994;71:584–7.

93. Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. Br J Gen Pract 1996;46:77–79.
94. National Kidney F: KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. American journal of kidney diseases: the official journal of the National Kidney Foundation 2012;60:850-86.
95. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787-847.
96. Ezekowitz J, McAlister FA, Humphries KH, Norris CM, Tonelli M, Ghali WA, *et al.* The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am Coll Cardiol. 2004;44:1587-92.
97. Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, *et al*. Effects of enalapril in systolic heart failure patients with and without CKD: insights from the SOLVD Treatment trial. Int J Cardiol. 2013;167:151-6.
98. Yusuf S, Pfeffer M A, Swedberg K. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777–81.
99. Massie BM, Carson PE, McMurray JJ. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456–67.
100. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J*, et al*. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27:2338-45.

101. Patel K, Fonarow GC, Kitzman DW, Aban IB, Love TE, Allman RM, *et al.* Angiotensin receptor blockers and outcomes in real-world older patients with heart failure and preserved ejection fraction: a propensity-matched inception cohort clinical effectiveness study. Eur J Heart Fail. 2012;14:1179-88.
102. Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? Insights from 254,301 patients from randomized trials. Mayo Clinic Proc. 2016;91:51–60.
103. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, *et al*. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. Am J Kidney Dis. 2016;67:728-41.
104. Atkinson AB, Brown JJ, Cumming AM, Fraser R, Lever AF, Leckie BJ, *et al.* Captopril in the management of hypertension with renal artery stenosis: its long-term effect as a predictor of surgical outcome. Am J Cardiol. 1982;49:1460-6.
105. Raine AEG, Ledingham JGG. Clinical experience with captopril in the treatment of severe drug-resistant hypertension. Am J Cardiol. 1982;49:1475-9.
106. Kjekshus J, Swedberg K. Tolerability of enalapril in congestive heart failure. Am J Cardiol. 1988;62:67A-72.
107. White WB, Aydelotte ME. Clinical experience with labetalol and enalapril in combination in patients with severe essential and renovascular hypertension. Am J Med Sci. 1988;296:187-91.
108. Abraham PA, Opsahl JA, Halstenson CE, Keane WF. Efficacy and renal effects of enalapril therapy for hypertensive patients with chronic renal insufficiency. Arch Intern Med. 1988;148:2358-62.
109. Jackson B, Cubela RB, Conway EL, Johnston CI. Lisinopril pharmacokinetics in chronic renal failure. Br J Clin Pharmacol. 1988;25:719-24.

110. August P, Cody RJ, Sealey JE, Laragh JH. Hemodynamic responses to converting enzyme inhibition in patients with renal disease. Am J Hypertens. 1989;2:599-603.
111. Carlsen JE, Hansen FM, Jensen H. Efficacy and safety of cilazapril in hypertensive patients with moderate to severe renal impairment. Am J Med. 1989;87:79S-82.
112. Heeg JE, de Jong PE, de Zeeuw D. Additive antiproteinuric effect of the NSAID indomethacin and the ACE inhibitor lisinopril.Am J Nephrol. 1990;10:94-7.
113. Zanella MT, Salgado BJL, Kohlmann O, Ribeiro AB. Angiotensin-converting enzyme (ACE) inhibition: therapeutic option for diabetic hypertensive patients. Drugs.1990;39:33-9.
114. de Jong PE, Apperloo AJ, Heeg JE, de Zeeuw D. Lisinopril in hypertensive patients with renal function impairment. Nephron. 1990;55:43-8.
115. Apperloo AJ, de Zeeuw D, Sluiter HE, de Jong PE. Differential effects of enalapril and atenolol on proteinuria and renal haemodynamics in non-diabetic renal disease. BMJ. 1991;303:821-4.
116. Kamper AL, Strandgaard S, Leyssac PP. Effect of enalapril on the progression of chronic renal failure: a randomized control trial.Am J Hypertens. 1992;5:423-30.
117. Bauer JH, Reams GP, Hewett J. A randomized, double-blind, placebocontrolled trial to evaluate the effect of enalapril in patients with clinical diabetic nephropathy. Am J Kidney Dis. 1992;20:443-57.
118. Ferder L, Daccordi H, Martello M, Panzalis M, Inserra F. Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. Hypertension. 1992;19(2):I237-42.
119. Dahlstrom U, Karlsson E. Captopril and spironolactone therapy for refractory congestive heart failure. Am J Cardiol. 1993;71:29A-33.

120. Hannedouche T, Landais P, Goldfarb B. Randomised controlled trial of enalapril and beta-blockers in non-diabetic chronic renal failure. BMJ. 1994;309:833-7.
121. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med. 1998;158:26–32.
122. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med. 2000;160:685–93.
123. Weir MR, Lakkis JI, Jaar B. Use of renin-angiotensin system blockade in advanced CKD: an NKF-KDOQI controversies report. Am J Kidney Dis. 2018;72:873–84.
124. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD. Kidney Int. 2020;98:S1-115.
125. Mahmoudpour SH, Asselbergs FW, Souverein PC, de Boer A, Maitland-van der Zee AH. Prescription patterns of angiotensin-converting enzyme inhibitors for various indications: A UK population-based study. Br J Clin Pharmacol. 2018;84:2365-72.
126. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, *et al.* Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113:671-8.
127. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, CKD, and the effect of an angiotensin receptor blocker in addition to an angiotensin converting enzyme inhibitor in patients with moderate to severe heart failure. Circulation. 2009;120:1577-84.
128. Sharma P, Blackburn RC, Parke CL, McCullough K, Marks A, Black C. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic CKD. Cochrane Database Syst Rev. 2011;10:CD007751.

129. Ahmed A, Love TE, Sui X, Rich MW. Effects of angiotensin-converting enzyme inhibitors in systolic heart failure patients with CKD: a propensity score analysis. J Card Fail. 2006;12:499-506.
130. Gibney EM, Casebeer AW, Schooley LM. Cardiovascular medication use after coronary bypass surgery in patients with renal dysfunction: a national Veterans Administration study. Kidney Int. 2005;68:826-32.
131. Ahmed A, Centor RM, Weaver MT, Perry GJ. A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. Am Heart J. 2005;149:737-43.
132. Reinecke H, Matzkies F, Fobker M, Breithardt G, Schaefer RM. Diabetic nephropathy, percutaneous coronary interventions, and blockade of the renin-angiotensin system. Cardiology. 2005;104:24-30.
133. So WY, Ozaki R, Chan NN. Effect of angiotensin-converting enzyme inhibition on survival in 3773 Chinese type 2 diabetic patients. Hypertension. 2004;44:294-9.
134. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109:1004-9.
135. Ruggenenti P, Iliev I, Costa GM, Parvanova A, Perna A, Giuliano GA*, et al.* Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 diabetes: a prespecified analysis of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). Diabetes Care. 2008;31:1629-34.
136. Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, *et al*. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic

dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Circulation. 1993;88:2277-83.

137. Sutton MG, Sharpe N. Left ventricular remodelling after myocardial infarction: pathophysiology and therapy. Circulation. 2000;101:2981-8.

138. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329:1456-62.

139. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851-60.

140. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861-9.

SR NO	NAME	CR NO	AGE	SEX	CKD STAGE	CAUSE OF CKD	COMORBIDITIES	CHF	EJECTION FRACTION	SYSTOLIC/ DIALSTOLIC CHF	SBP	DBP	B UREA	CREATININE	POTTASIUM	UPCR	eGFR	INDICATION OF TREATMENT
1	SK	316434	45	F	3	DKD	HTN,T2DM	NO	60	NO	150	90	63	1.87	3.06	1	33	PROTEINURIC CKD
2	RG	893880	58	M	4	DKD	HTN,T2DM,CAD	YES	45	SYSTOLIC	140	90	69	3.16	5.3	0.82	22	PROTEINURIC CKD+ CHF
3	MK	1160736	55	F	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	183	2.34	5.2	1.9	23	PROTEINURIC CKD
4	KS	1027131	38	M	4	DKD	HTN,T2DM,CAD	YES	40	SYSTOLIC	140	90	69	3.7	5.3	0.82	17	PROTEINURIC CKD+ CHF
5	AG	1088377	59	M	4	DKD	HTN,T2DM	NO	60	NO	130	90	61	3.8	4.96	2.2	16	PROTEINURIC CKD
6	BS	27466	67	M	4	CGN	HTN	NO	60	NO	130	90	108	2.9	4.84	0.82	23	PROTEINURIC CKD
7	CJ	990160	34	M	3	CGN	HTN	NO	60	NO	140	90	98	2.2	5.1	1.6	31	PROTEINURIC CKD
8	SK	665189	39	F	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	38	2.11	4.31	4.92	32	PROTEINURIC CKD
9	GK	443654	73	F	4	DKD	HTN,T2DM,CAD	YES	60	DIASTOLIC	120	90	91	2.87	4.99	0.86	17	PROTEINURIC CKD+ CHF
10	KN	1122372	64	F	4	DKD	HTN,T2DM,CAD	YES	58	DIASTOLIC	130	90	72	2.63	5.14	1.46	20	PROTEINURIC CKD+ CHF
11	MS	1115714	64	M	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	47	2.24	4.9	1.26	32	PROTEINURIC CKD
12	KR	1088356	69	F	4	DKD	HTN,T2DM,CAD	YES	42	SYSTOLIC	120	90	61	3.63	5.02	2.08	16	PROTEINURIC CKD+ CHF
13	SR	1125027	66	M	4	DKD	HTN,T2DM	NO	60	NO	140	90	106	3.73	4.39	1.26	17	PROTEINURIC CKD
14	AK	1122268	50	M	4	NOT KNOWN	CAD	YES	40	BOTH	130	90	157	2.82	5.32	1.26	26	PROTEINURIC CKD+ CHF
15	SG	1129743	65	M	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	140	90	53	2.56	4.7	2.63	27	PROTEINURIC CKD
16	TRS	770974	66	M	4	DKD	HTN,T2DM	NO	60	NO	140	90	95	4.04	5.1	3.6	16	PROTEINURIC CKD
17	SK	1132399	69	M	4	DKD	HTN,T2DM	YES	60	DIASTOLIC	150	90	237	3.2	3.3	4.46	20	PROTEINURIC CKD+ CHF
18	MS	1134998	60	M	4	NOT KNOWN	HTN,CAD	YES	30	SYSTOLIC	130	90	57	3.26	4.11	2.8	21	PROTEINURIC CKD+ CHF
19	RL	1150641	58	M	3	RENAL CALCULUS DISEASE	HTN	NO	60	NO	140	90	41	1.93	4.85	2.6	40	PROTEINURIC CKD
20	P	361795	47	M	4	DKD	HTN,T2DM,CAD	NO	60	NO	130	90	56	3.61	4.73	9.4	20	PROTEINURIC CKD
21	BL	1137729	56	M	4	DKD	HTN,T2DM	YES	36	SYSTOLIC	140	90	92	4.12	4.48	9.26	16	PROTEINURIC CKD+ CHF
22	TK	1135202	44	M	3	CGN	HTN	NO	60	NO	130	90	57	1.83	4.59	6.02	47	PROTEINURIC CKD
23	MS	1144317	63	M	4	DKD	T2DM,CAD	YES	32	SYSTOLIC	110	90	110	3.08	4.16	6.46	22	PROTEINURIC CKD+ CHF
24	VD	1147195	59	M	4	DKD	HTN,T2DM	YES	48	SYSTOLIC	130	90	111	3.7	4.2	9.7	18	PROTEINURIC CKD+ CHF
25	MB	1140085	50	F	3	NOT KNOWN	NONE	YES	42	SYSTOLIC	120	90	66	1.82	3.46	1.88	33	PROTEINURIC CKD+ CHF
26	SS	460847	50	M	4	DKD	HTN,T2DM	YES	60	BOTH	130	90	92	3.57	3.42	0.366	20	CHF
27	GK	932365	66	F	3	NOT KNOWN	NONE	YES	28	SYSTOLIC	140	90	106	1.77	4.1	0.92	42	PROTEINURIC CKD+ CHF
28	N	1114576	72	F	3	DKD	NONE	NO	60	NO	120	90	68	1.78	5.2	6.8	30	PROTEINURIC CKD
29	UR	1010641	51	F	3	NOT KNOWN	NONE	NO	60	NO	130	90	39	1.75	4.2	6.7	35	PROTEINURIC CKD
30	RS	1152348	46	F	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	140	90	122	2.18	4.9	2.8	28	PROTEINURIC CKD
31	S	360835	68	F	4	NOT KNOWN	NONE	YES	28	SYSTOLIC	120	90	98	3.13	4.75	0.92	16	CHF
32	P	140746	57	F	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	107	3.2	4.76	12.8	16	PROTEINURIC CKD
33	KS	1027131	48	M	4	NOT KNOWN	NONE	YES	60	DIASTOLIC	120	90	69	3.7	5.08	5.26	19	PROTEINURIC CKD+ CHF
34	S	911509	64	M	4	DKD	HTN,T2DM	NO	60	NO	140	90	79	3.6	3.9	12.9	16	PROTEINURIC CKD
35	SK	1086481	35	M	3	CGN	HTN	NO	60	NO	140	90	50	2.47	5.1	15	34	PROTEINURIC CKD
36	HK	1081937	55	F	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	24	1.79	3.9	2.26	33	PROTEINURIC CKD
37	SK	303069	56	F	4	NOT KNOWN	CAD	YES	28	SYSTOLIC	120	90	95	2.37	3.11	0.16	23	CHF
38	JS	1034225	20	M	4	CGN	HTN	NO	60	NO	130	90	117	4.32	3.98	2.3	19	PROTEINURIC CKD
39	SKK	875816	47	F	4	DKD	HTN,T2DM,CAD	YES	32	SYSTOLIC	140	90	95	3.03	5.1	6.9	18	PROTEINURIC CKD+ CHF
40	KS	162410	65	M	3	DKD	HTN,T2DM	YES	30	SYSTOLIC	130	90	38	1.75	4.78	0.34	43	CHF
41	AS	1056543	38	M	3	NOT KNOWN	CAD	YES	60	DIASTOLIC	120	90	65	2.2	4.5	0.39	32	CHF
42	DK	1070515	40	F	4	DKD	HTN,T2DM	NO	60	NO	140	90	79	2.15	4.74	0.8	29	PROTEINURIC CKD
43	SP	979897	40	M	3	IGA NEPHROPATHY	HTN	NO	60	NO	130	90	43	1.98	4.3	1	43	PROTEINURIC CKD
44	SK	1073465	53	F	4	DKD	T2DM	YES	40	SYSTOLIC	120	90	99	3.02	3.47	0.54	17	CHF
45	BS	1048563	49	M	3	DKD	T2DM,HTN	NO	60	NO	130	90	151	2.3	4.5	12.3	34	PROTEINURIC CKD
46	SS	898912	64	M	3	DKD	T2DM,HTN	NO	60	NO	130	90	105	2.54	5.1	3.65	27	PROTEINURIC CKD
47	S	401188	53	F	4	DKD	T2DM,HTN	NO	60	NO	130	90	73	2.9	3.9	5.13	19	PROTEINURIC CKD
48	SK	1087937	42	M	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	91	4.11	4.8	7.6	18	PROTEINURIC CKD
49	SK	40724	49	F	3	HTN NEPHROSCLEROSIS	HTN	YES	38	SYSTOLIC	130	90	56	1.69	4.9	1.43	36	PROTEINURIC CKD+ CHF
50	RK	1129764	50	F	3	CGN	HTN	NO	60	NO	140	90	96	1.39	4.6	1.6	46	PROTEINURIC CKD
51	SK	1149941	58	F	3	NOT KNOWN	NONE	YES	58	DIASTOLIC	120	90	40	1.76	4.48	1.9	44	PROTEINURIC CKD+ CHF

SR NO	NAME	CR NO	ALREADY TAKING DRUG AT ENROLMENT	DRUG	DOSAGE	FREEQUENCY	DURATION OF DRUG USAGE	ANY PREVIOUS COMPLICATION	DRUG PRECSRIBED	DOSAGE	FREEQUENCY	Dose increased	FREEQUENCY	TOTAL DURATION OF INCREASED DOSE	NO OF FOLLOW UP
1	SK	316434	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
2	RG	893880	YES	TELMISARTAN	40	ONCE A DAY	12 MONTHS	NONE	-	-	-	-	-	-	5
3	MK	1160736	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	4
4	KS	1027131	YES	ENALAPRIL	5	ONCE A DAY	6 MONTHS	NONE	-	-	-	10	ONCE DAILY	5 MONTHS	6
5	AG	1088377	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	6
6	BS	27466	YES	TELMISARTAN	40	TWICE ADAY	12 MONTHS	AKI	-	-		-	-	-	7
7	CJ	990160	YES	ENALAPRIL	5	TWICE ADAY	8 MONTHS	NONE	-	-	-	-	-	-	7
8	SK	665189	NO	-	-	-	-	-	ENALAPRIL	10	ONCE DAILY	-	-	-	8
9	GK	443654	YES	RAMIPRIL	2.5	ONCE A DAY	12 MONTHS	NONE	-	-	-	-	-	-	5
10	KN	1122372	YES	TELMISARTAN	40	ONCE A DAY	15 MONTHS	NONE	-	-	-	-	-	-	5
11	MS	1115714	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
12	KR	1088356	NO	-	-	-	-	-	RAMIPRIL	2.5	ONCE DAILY	-	-	-	4
13	SR	1125027	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	1
14	AK	1122268	YES	ENALAPRIL	10	ONCE A DAY	6 MONTHS	HYPERKALEMIA	-	-	-	-	-	-	8
15	SG	1129743	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
16	TRS	770974	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	2
17	SK	1132399	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	5
18	MS	1134998	YES	ENALAPRIL	5	ONCE A DAY	9MONTHS	NONE	-	-	-	-	-	-	8
19	RL	1150641	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	3
20	P	361795	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
21	BL	1137729	YES	TELMISARTAN	40	ONCE A DAY	6 MONTHS	NONE	-	-	-	-	-	-	8
22	TK	1135202	YES	ENALAPRIL	5	ONCE A DAY	2 MONTHS	AKI	-	-	-	-	-	-	8
23	MS	1144317	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	5
24	VD	1147195	YES	TELMISARTAN	40	ONCE A DAY	12 MONTHS	NONE	-	-	-	-	-	-	7
25	MB	1140085	YES	TELMISARTAN	40	ONCE A DAY	5 MONTHS	NONE	-	-	-	-	-	-	7
26	SS	460847	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	8
27	GK	932365	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	80	ONCE DAILY	3 MONTHS	8
28	N	1114576	YES	ENALAPRIL	5	ONCE A DAY	3 MONTHS	NONE	-	-	-	-	-	-	8
29	UR	1010641	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	4
30	RS	1152348	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	10	ONCE DAILY	2 MONTHS	7
31	S	360835	YES	TELMISARTAN	40	ONCE A DAY	2 MONTHS	AKI	-	-	-	-	-	-	8
32	P	140746	NO	-	-	-	-	-	RAMIPRIL	2.5	ONCE DAILY	-	-	-	5
33	KS	1027131	YES	RAMIPRIL	2.5	ONCE A DAY	8 MONTHS	NONE	-	-	-	5	ONCE DAILY	1 MONTH	8
34	S	911509	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	2
35	SK	1086481	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	80	ONCE DAILY	2 MONTHS	8
36	HK	1081937	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	80	ONCE DAILY	3 MONTHS	9
37	SK	303069	YES	RAMIPRIL	2.5	ONCE A DAY	10 MONTHS	NONE	-	-	-	-	-	-	8
38	JS	1034225	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	2
39	SKK	875816	NO	-	-	-	-	-	RAMIPRIL	2.5	ONCE DAILY	-	-	-	5
40	KS	162410	YES	RAMIPRIL	2.5	ONCE A DAY	5 MONTHS	NONE	-	-	-	-	-	-	9
41	AS	1056543	YES	TELMISARTAN	40	ONCE A DAY	2 MONTHS	NONE	-	-	-	-	-	-	8
42	DK	1070515	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
43	SP	979897	YES	TELMISARTAN	40	ONCE A DAY	3 MONTHS	NONE	-	-	-	-	-	-	8
44	SK	1073465	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	6
45	BS	1048563	NO	-	-	-	-	-	RAMIPRIL	2.5	ONCE DAILY	-	-	-	8
46	SS	898912	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
47	S	401188	YES	RAMIPRIL	2.5	ONCE A DAY	4 MONTHS	AKI	-	-	-	-	-	-	7
48	SK	1087937	NO	-	-	-	-	-	RAMIPRIL	2.5	ONCE DAILY	-	-	-	5
49	SK	40724	YES	TELMISARTAN	40	ONCE A DAY	1 MONTH	NONE	-	-	-	-	-	-	7
50	RK	1129764	YES	TELMISARTAN	40	ONCE A DAY	2 MONTHS	NONE	-	-	-	-	-	-	8
51	SK	1149941	NO	-	-	-	-	-	RAMIPRIL	5	ONCE DAILY	10	ONCE DAILY	3 MONTHS	7

SR NO	NAME	CR NO	B UREA followup	CREATININE followup	POTTASIUM followup	UPCR followup	eGFR followup	CKD STAGE followup	CHANGE IN DRUG DOSAGE	BETA BLOCKERS	ADVERSE EVENTS	EVENT PRECEDING DISCOUNTINUATION OF DRUG	TOTAL DURATION OF DRUG INTAKE
1	SK	316434	72	3.8	3.96	0.86	19	4	NO	YES	AKI	NONE	6 MONTHS
2	RG	893880	76	2.4	5.07	0.91	30	3	NO	YES	NO	NONE	6 MONTHS
3	MK	1160736	327	5.7	6.7	1.48	8	5	NO	YES	HYPERKALEMIA,AKI	EXPIRED	3 MONTHS
4	KS	1027131	80	3.79	5.1	0.542	17	4	YES, INCREASED ONCE	YES	NO	NONE	6 MONTHS
5	AG	1088377	98	5.22	4.73	2.2	12	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR	5 MONTHS
6	BS	27466	108	2.8	4.82	0.29	24	4	NO	YES	NO	NONE	6 MONTHS
7	CJ	990160	53	2.02	5.13	0.26	36	3	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
8	SK	665189	36	1.89	4.15	3.04	36	3	NO	NO	NO	NONE	6 MONTHS
9	GK	443654	102	2.68	3.56	1.06	18	4	NO	NO	NO	NONE	6 MONTHS
10	KN	1122372	68	3.04	3.53	0.94	17	4	NO	NO	NO	NONE	6 MONTHS
11	MS	1115714	58	1.58	5.39	0.44	49	3	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
12	KR	1088356	79	4.87	5.3	1.86	9	5	NO	YES	HYPERKALEMIA	WORSENING OF GFR	2 MONTHS
13	SR	1125027	106	5.37	5.7	1.22	11	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR	15 DAYS
14	AK	1122268	165	2.69	4.69	1.2	28	4	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
15	SG	1129743	88	2.39	5.5	3	29	4	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
16	TRS	770974	105	6.5	7.11	4.74	9	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR, HYPERKALEMIA	1 MONTH
17	SK	1132399	211	5.59	3.21	4.02	10	5	NO	YES	AKI	EXPIRED	2 MONTHS
18	MS	1134998	65	3.23	4.2	2	21	4	NO	NO	NO	NONE	6 MONTHS
19	RL	1150641	44	1.68	4.8	2.09	40	3	NO	NO	NO	NONE	6 MONTHS
20	P	361795	132	5.35	3.4	8.7	12	5	NO	NO	AKI	NONE	6 MONTHS
21	BL	1137729	95	4.06	4.01	15.2	16	4	NO	YES	NO	NONE	6 MONTHS
22	TK	1135202	36	1.43	4.49	1.04	62	2	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
23	MS	1144317	135	4.96	4.64	6.78	12	5	NO	YES	AKI	WORSENING OF GFR	4 MONTHS
24	VD	1147195	121	5.75	4.35	4.8	11	5	NO	YES	AKI	NONE	6 MONTHS
25	MB	1140085	80	2.07	4.08	2.02	29	4	NO	NO	AKI	EXPIRED	5 MONTHS
26	SS	460847	61	2.54	3.53	0.59	30	3	NO	YES	NO	NONE	6 MONTHS
27	GK	932365	60	1.13	4.6	0.46	72	2	YES, INCREASED ONCE	YES	NO	NONE	6 MONTHS
28	N	1114576	68	1.45	4.2	5.4	38	3	NO	YES	NO	NONE	6 MONTHS
29	UR	1010641	55	2.21	6.5	4.3	26	4	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR, HYPERKALEMIA	2 MONTHS
30	RS	1152348	126	2.08	4.72	1.62	29	4	YES, INCREASED ONCE	YES	NO	NONE	6 MONTHS
31	S	360835	95	3.08	4.6	0.68	16	4	NO	YES	AKI	EXPIRED	5 MONTHS
32	P	140746	133	5.29	5.9	11.6	9	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR, HYPERKALEMIA	4 MONTHS
33	KS	1027131	106	4.25	4.66	4.89	17	4	YES, INCREASED ONCE	YES	AKI	NONE	6 MONTHS
34	S	911509	69	3.2	4.5	7.6	21	4	NO	NO	NO	EXPIRED	1 MONTH
35	SK	1086481	63	1.73	5.2	9.4	52	3	YES, INCREASED ONCE	NO	NO	NONE	6 MONTHS
36	HK	1081937	51	1.42	3.84	2.08	44	3	YES, INCREASED ONCE	YES	NO	NONE	6 MONTHS
37	SK	303069	108	1.86	3.85	0.198	31	4	NO	NO	NO	NONE	6 MONTHS
38	JS	1034225	105	5.3	4.9	2.08	15	5	NO	NO	AKI	EXPIRED	15 DAYS
39	SKK	875816	109	4.84	6.4	7.1	11	5	NO	YES	HYPERKALEMIA,AKI	EXPIRED	2 MONTHS
40	KS	162410	63	1.78	4.5	0.39	43	3	NO	YES	NO	NONE	6 MONTHS
41	AS	1056543	66	2.15	4.29	0.33	33	3	NO	YES	NO	EXPIRED	4 MONTHS
42	DK	1070515	76	2.06	4.48	0.7	31	4	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
43	SP	979897	38	1.58	4.24	0.4	56	3	NO	NO	NO	NONE	6 MONTHS
44	SK	1073465	97	3.69	4.04	0.3	14	5	NO	YES	NO	EXPIRED	5 MONTHS
45	BS	1048563	129	1.78	4.3	5.45	46	3	NO	YES	NO	NONE	6 MONTHS
46	SS	898912	98	2.49	5.1	3.68	28	4	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
47	S	401188	122	3.4	4.36	2.9	16	4	NO	NO	NO	NONE	6 MONTHS
48	SK	1087937	106	4.7	4.88	7.6	18	4	NO	NO	HYPERKALEMIA	HYPERKALEMIA	5 MONTHS
49	SK	40724	56	1.31	4.4	1.63	49	3	NO	NO	NO	HYPERKALEMIA	4 MONTHS
50	RK	1129764	76	1.4	4.9	1.45	46	3	NO	YES	NO	NONE	6 MONTHS
51	SK	1149941	48	1.59	4.3	1.47	50	3	YES, INCREASED ONCE	NO	NO	NONE	6 MONTHS

SR NO	NAME	CR NO	AGE	SEX	CKD STAGE	CAUSE OF CKD	COMORBIDITIES	CHF	EJECTION FRACTION	SYSTOLIC/ DIALSTOLIC CHF	SBP	DBP	B UREA	CREATININE	POTTASIUM	UPCR	eGFR	INDICATION OF TREATMENT
52	BLG	1120305	65	M	4	DKD	HTN,T2DM	NO	60	NO	140	90	106	2.73	4.49	2.46	25	PROTEINURIC CKD
53	SK	102925	72	M	4	DKD	T2DM,CAD	YES	22	SYSTOLIC	120	90	91	2.86	4.9	1.84	22	PROTEINURIC CKD+ CHF
54	SK	978857	66	F	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	130	90	91	2.87	4.5	4.29	18	PROTEINURIC CKD
55	KN	1122372	64	F	4	DKD	HTN,T2DM	NO	60	NO	140	90	72	2.63	5.1	3.84	20	PROTEINURIC CKD
56	GK	443654	73	F	4	DKD	HTN,T2DM	YES	28	SYSTOLIC	120	90	91	2.8	4.9	3.11	17	PROTEINURIC CKD+ CHF
57	S	665189	39	F	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	140	90	38	2.11	4.3	1.49	31	PROTEINURIC CKD
58	GS	960984	43	M	4	NOT KNOWN	NONE	NO	60	NO	130	90	92	3.57	3.4	4.6	21	PROTEINURIC CKD
59	MC	967302	49	M	4	DKD	HTN,T2DM	NO	60	NO	130	90	56	3.6	4.62	2.87	20	PROTEINURIC CKD
60	HSB	985693	77	M	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	140	90	101	3.7	5.1	5.6	16	PROTEINURIC CKD
61	B	994700	60	M	3	DKD	HTN,T2DM	NO	60	NO	140	90	57	1.8	4.58	0.94	40	PROTEINURIC CKD
62	ND	287302	48	F	4	DKD	N,RENAL CALCULUS	NO	60	NO	130	90	112	2.6	5.1	7.6	22	PROTEINURIC CKD
63	TS	984257	60	F	3	RENAL CALCULUS DISEASE	HTN	YES	34	SYSTOLIC	120	90	46	1.72	4.48	0.26	34	CHF
64	JG	936367	66	F	3	NOT KNOWN	NONE	YES	28	SYSTOLIC	140	90	106	1.77	4.1	0.92	42	PROTEINURIC CKD+ CHF
65	SS	460845	50	M	4	DKD	HTN,T2DM	YES	58	DIASTOLIC	130	90	92	3.57	3.42	0.366	20	CHF
66	BS	1004322	48	M	3	DKD	HTN,T2DM	YES	38	SYSTOLIC	130	90	56	2.3	4.5	0.78	34	PROTEINURIC CKD+ CHF
67	HS	462860	67	M	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	140	90	36	1.86	5.08	1.2	44	PROTEINURIC CKD
68	JS	1006816	36	M	4	RENAL CALCULUS DISEASE	HTN	NO	60	NO	140	90	68	3.53	5.1	5.2	22	PROTEINURIC CKD
69	KS	1005121	55	M	4	DKD	HTN,T2DM	NO	60	NO	130	90	74	3.92	3.9	4.62	17	PROTEINURIC CKD
70	S	175704	33	M	4	NOT KNOWN	NONE	NO	60	NO	120	90	118	3.92	5	7.8	20	PROTEINURIC CKD
71	RG	707703	56	M	4	DKD	HTN,T2DM,CAD	NO	60	NO	140	90	56	3.8	4.86	4.6	17	PROTEINURIC CKD
72	SR	1008616	50	F	4	RENAL CALCULUS DISEASE	HTN	NO	60	NO	150	90	60	2.92	4.48	5.6	24	PROTEINURIC CKD
73	MS	1011937	57	M	4	NOT KNOWN	NONE	NO	60	NO	120	90	102	2.9	5.1	9.2	22	PROTEINURIC CKD
74	KK	1000294	60	M	4	HTN NEPHROSCLEROSIS	HTN,CAD	YES	38	SYSTOLIC	140	90	60	2.8	4.48	5.6	24	PROTEINURIC CKD+ CHF
75	ML	915683	40	M	4	DKD	HTN,T2DM	YES	44	SYSTOLIC	130	90	102	3.12	4.76	0.54	25	CHF
76	RM	985810	55	F	4	DKD	HTN,T2DM	YES	60	DIASTOLIC	120	90	61	2.44	4.46	1.69	23	PROTEINURIC CKD+ CHF
77	KS	1009720	53	M	4	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	64	4.2	5.1	3.9	16	PROTEINURIC CKD
78	RS	997239	68	M	4	RENAL CALCULUS DISEASE	HTN	NO	60	NO	140	90	60	3.96	4.2	4.26	16	PROTEINURIC CKD
79	MN	1017054	48	M	3	NOT KNOWN	NONE	YES	48	SYSTOLIC	120	80	40	1.76	4.15	0.18	47	CHF
80	SD	1150829	62	F	4	DKD	HTN,T2DM,CAD	NO	60	NO	130	90	64	2.94	4.4	4.6	18	PROTEINURIC CKD
81	CJ	990160	64	M	4	ANCA VASCULITIS	HTN	NO	60	NO	140	90	123	2.34	5.1	1.2	29	PROTEINURIC CKD
82	SK	316434	45	F	3	DKD	HTN, T2DM	NO	60	NO	140	90	63	2.1	3.7	1.42	29	PROTEINURIC CKD
83	RG	893880	48	M	4	DKD	HTN,T2DM	NO	60	NO	130	90	69	3.16	5.1	2.6	23	PROTEINURIC CKD
84	MK	1160736	38	F	4	NOT KNOWN	NONE	NO	60	NO	120	90	183	3.34	5	1.9	17	PROTEINURIC CKD
85	SS	1166321	68	M	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	52	1.94	4.35	0.9	39	PROTEINURIC CKD
86	KS	1027131	38	M	4	DKD	HTN, T2DM	NO	60	NO	140	90	69	3.7	5	2.11	21	PROTEINURIC CKD
87	AKG	1088377	59	M	4	DKD	HTN, T2DM	NO	58	NO	150	90	61	3.9	4.9	4.17	17	PROTEINURIC CKD
88	BS	27466	67	M	4	DKD	HTN,T2DM	NO	60	NO	140	90	104	2.9	4.84	1.66	23	PROTEINURIC CKD
89	SM	110778	55	F	3	DKD	T2DM	YES	60	DIASTOLIC	130	90	92	2.17	4.9	0.98	35	PROTEINURIC CKD+ CHF
90	IS	789016	50	M	3	DKD	HTN,T2DM	NO	58	NO	140	90	125	2.56	4.9	1	30	PROTEINURIC CKD
91	AY	1141366	50	M	4	DKD	HTN, T2DM	NO	60	NO	150	90	44	2.67	4.72	1	29	PROTEINURIC CKD
92	BL	1014512	66	M	4	DKD	HTN,T2DM	NO	60	NO	140	90	50	2.18	5.1	1.6	33	PROTEINURIC CKD
93	NS	1066501	51	M	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	90	62	2.4	3.52	1.1	31	PROTEINURIC CKD
94	GSR	1019722	83	M	3	DKD	HTN,T2DM,CAD	YES	42	SYSTOLIC	120	90	58	1.87	4.5	0.8	37	PROTEINURIC CKD+ CHF
95	PC	765901	72	M	3	DKD	HTN,T2DM	NO	60	NO	130	90	68	1.46	3.92	1.5	51	PROTEINURIC CKD
96	J	556071	58	M	3	HTN NEPHROSCLEROSIS	HTN	NO	60	NO	150	100	72	1.48	4.46	1.8	55	PROTEINURIC CKD
97	HD	733827	68	M	3	NOT KNOWN	NONE	YES	24	SYSTOLIC	120	90	47	1.51	4.2	0.4	50	CHF
98	JK	357061	64	F	4	DKD	HTN, T2DM	NO	60	NO	140	90	52	2.18	4.6	1.7	25	PROTEINURIC CKD
99	MK	343055	76	M	3	DKD	HTN, T2DM	NO	58	NO	130	90	60	1.71	4.9	1.1	41	PROTEINURIC CKD
100	RS	157581	21	F	4	FSGS	HTN	NO	60	NO	130	90	132	3.22	5.1	4.16	20	PROTEINURIC CKD

SR NO	NAME	CR NO	ALREADY TAKING DRUG AT ENROLMENT	DRUG	DOSAGE	FREEQUENCY	DURATION OF DRUG USAGE	ANY PREVIOUS COMPLICATION	DRUG PRECSRIBED	DOSAGE	FREEQUENCY	Dose increased	FREEQUENCY	TOTAL DURATION OF INCREASED DOSE	NO OF FOLLOW UP
52	BLG	1120305	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	4
53	SK	102925	YES	TELMISARTAN	40	ONCE A DAY	6 MONTHS	NONE	-	-	-	-	-	-	8
54	SK	978857	NO	-	-	-	-	-	ENALAPRIL	10	ONCE DAILY	-	-	-	8
55	KN	1122372	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
56	GK	443654	YES	RAMIPRIL	2.5	ONCE A DAY	1 MONTH	HYPERKALEMIA	-	-	-	-	-	-	8
57	S	665189	NO	-	-	-	-	-	ENALAPRIL	10	ONCE DAILY	-	-	-	8
58	GS	960984	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
59	MC	967302	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	5
60	HSB	985693	NO	-	-	-	-	-	RAMIPRIL	2.5	ONCE DAILY	-	-	-	3
61	B	994700	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	4
62	ND	287302	NO	-	-	-	-	-	ENALAPRIL	10	ONCE DAILY	-	-	-	6
63	TS	984257	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
64	JG	936367	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	80	ONCE DAILY	4 MONTHS	8
65	SS	460845	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	8
66	BS	1004322	YES	TELMISARTAN	40	ONCE A DAY	4 MONTHS	NONE	-	-	-	-	-	-	8
67	HS	462860	NO	-	-	-	-	-	ENALAPRIL	10	ONCE DAILY	-	-	-	7
68	JS	1006816	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	9
69	KS	1005121	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	3
70	S	175704	NO	-	-	-	-	-	RAMIPRIL	5	ONCE DAILY	-	-	-	7
71	RG	707703	YES	TELMISARTAN	40	ONCE A DAY	12 MONTHS	NONE	-	-	-	-	-	-	3
72	SR	1008616	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
73	MS	1011937	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	5
74	KK	1000294	YES	RAMIPRIL	5	ONCE A DAY	3 MONTHS	NONE	-	-	-	-	-	-	7
75	ML	915683	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	8
76	RM	985810	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
77	KS	1009720	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
78	RS	997239	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	4
79	MN	1017054	YES	RAMIPRIL	2.5	ONCE A DAY	1 MONTH	NONE	-	-	-	-	-	-	8
80	SD	1150829	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
81	CJ	990160	YES	TELMISARTAN	40	ONCE A DAY	12 MONTHS	HYPERKALEMIA	-	-	-	-	-	-	3
82	SK	316434	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
83	RG	893880	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	7
84	MK	1160736	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	4
85	SS	1166321	YES	ENALAPRIL	5	ONCE A DAY	5 MONTHS	NONE	-	-	-	-	-	-	9
86	KS	1027131	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
87	AKG	1088377	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	4
88	BS	27466	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
89	SM	110778	YES	ENALAPRIL	10	ONCE A DAY	3 MONTHS	HYPERKALEMIA	-	-	-	-	-	-	8
90	IS	789016	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	4
91	AY	1141366	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	5
92	BL	1014512	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8
93	NS	1066501	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	9
94	GSR	1019722	YES	RAMIPRIL	2.5	ONCE A DAY	4 MONTHS	NONE	-	-	-	-	-	-	8
95	PC	765901	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	5
96	J	556071	NO	-	-	-	-	-	ENALAPRIL	10	ONCE DAILY	-	-	-	6
97	HD	733827	YES	TELMISARTAN	40	ONCE A DAY	6 MONTHS	AKI	-	-	-	-	-	-	8
98	JK	357061	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	6
99	MK	343055	NO	-	-	-	-	-	ENALAPRIL	5	ONCE DAILY	-	-	-	7
100	RS	157581	NO	-	-	-	-	-	TELMISARTAN	40	ONCE DAILY	-	-	-	8

SR NO	NAME	CR NO	B UREA followup	CREATININE followup	POTTASIUM followup	UPCR followup	eGFR followup	CKD STAGE followup	CHANGE IN DRUG DOSAGE	BETA BLOCKERS	ADVERSE EVENTS	EVENT PRECEDING DISCOUNTINUATION OF DRUG	TOTAL DURATION OF DRUG INTAKE
52	BLG	1120305	128	4.15	6.7	1.06	15	5	NO	NO	HYPERKALEMIA,AKI	EXPIRED	3 MONTHS
53	SK	102925	102	2.56	3.34	0.84	26	4	NO	YES	NO	NONE	6 MONTHS
54	SK	978857	77	1.82	4.5	2.08	31	3	NO	NO	NO	NONE	6 MONTHS
55	KN	1122372	82	3.13	3.52	1.86	16	4	NO	NO	AKI	NONE	6 MONTHS
56	GK	443654	83	3.02	3.8	1.8	16	4	NO	YES	NO	NONE	6 MONTHS
57	S	665189	36	1.89	4.15	0.38	34	3	NO	YES	NO	NONE	6 MONTHS
58	GS	960984	110	1.96	3.64	1.08	43	3	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
59	MC	967302	132	5.35	3.4	2	12	5	NO	NO	AKI	WORSENING OF GFR	2 MONTHS
60	HSB	985693	121	5.7	6.1	2	10	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR, HYPERKALEMIA	3 MONTHS
61	B	994700	18	1.3	4.8	0.36	62	4	NO	NO	NO	OTHERS	4 MONTHS
62	ND	287302	106	4.7	4.29	2.94	11	5	NO	NO	AKI	EXPIRED	5 MONTHS
63	TS	984257	56	1.8	3.65	0.28	34	3	NO	YES	HYPERKALEMIA	HYPERKALEMIA	5 MONTHS
64	JG	936367	60	1.13	4.6	0.46	72	2	YES, INCREASED ONCE	YES	NO	NONE	6 MONTHS
65	SS	460845	61	2.54	3.53	0.59	30	3	NO	YES	NO	NONE	6 MONTHS
66	BS	1004322	43	2.1	4.8	0.28	38	3	NO	NO	NO	WORSENING OF GFR, HYPERKALEMIA	5 MONTHS
67	HS	462860	34	1.8	4.3	1.16	45	3	NO	YES	NO	NONE	6 MONTHS
68	JS	1006816	90	2.77	4.28	2.41	29	4	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
69	KS	1005121	109	4.75	4.5	2.84	14	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR	3 MONTHS
70	S	175704	96	3.9	4.46	2.7	20	4	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
71	RG	707703	46	3.8	5.6	5.39	17	4	NO	NO	HYPERKALEMIA	EXPIRED	2 MONTHS
72	SR	1008616	42	2.08	4.39	0.71	27	4	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
73	MS	1011937	128	4.92	4.2	6.9	12	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR	2 MONTHS
74	KK	1000294	42	2.9	4.39	4.8	24	4	NO	YES	NO	NONE	6 MONTHS
75	ML	915683	80	3.36	4.86	0.21	26	4	NO	NO	NO	NONE	6 MONTHS
76	RM	985810	48	2.56	4.26	1.2	22	4	NO	YES	NO	NONE	6 MONTHS
77	KS	1009720	58	4.8	4.9	2.16	14	5	NO	NO	NO	NONE	6 MONTHS
78	RS	997239	80	5.11	6.39	2.17	12	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR, HYPERKALEMIA	2 MONTHS
79	MN	1017054	40	1.6	4.48	0.26	53	4	NO	NO	NO	NONE	6 MONTHS
80	SD	1150829	97	3.2	4.3	2.8	16	4	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
81	CJ	990160	131	2.85	5.7	1.6	24	4	NO	NO	HYPERKALEMIA	EXPIRED	2 MONTHS
82	SK	316434	56	1.92	4.2	0.51	32	3	NO	NO	NO	NONE	6 MONTHS
83	RG	893880	58	2.98	4.64	1.7	25	4	NO	YES	HYPERKALEMIA	NONE	6 MONTHS
84	MK	1160736	282	5.04	6.3	1.82	11	5	NO	NO	HYPERKALEMIA,AKI	EXPIRED	2 MONTHS
85	SS	1166321	39	2.01	4.92	0.21	38	3	NO	NO	NO	NONE	6 MONTHS
86	KS	1027131	106	4.25	4.6	3.02	17	4	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
87	AKG	1088377	105	6.22	7.1	2.88	10	5	NO	NO	HYPERKALEMIA,AKI	WORSENING OF GFR, HYPERKALEMIA	2 MONTHS
88	BS	27466	121	2.8	5.01	0.8	24	4	NO	NO	NO	NONE	6 MONTHS
89	SM	110778	60	2.3	4.9	0.28	33	3	NO	NO	HYPERKALEMIA	HYPERKALEMIA	4 MONTHS
90	IS	789016	142	8	6.7	4.92	8	5	NO	NO	AKI	EXPIRED	4 MONTHS
91	AY	1141366	43	2.36	4.5	0.7	34	3	NO	NO	NO	NONE	6 MONTHS
92	BL	1014512	63	2.46	4.9	0.2	29	4	NO	NO	NO	NONE	6 MONTHS
93	NS	1066501	49	2.3	6.5	0.189	34	3	NO	NO	HYPERKALEMIA	HYPERKALEMIA	4 MONTHS
94	GSR	1019722	62	2.19	4.3	0.8	29	4	NO	YES	NO	NONE	6 MONTHS
95	PC	765901	42	2.8	4.5	1.6	23	4	NO	NO	AKI	WORSENING OF GFR	3 MONTHS
96	J	556071	58	1.9	4.3	1.11	40	3	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
97	HD	733827	40	1.6	4.8	0.32	49	3	NO	YES	NO	NONE	6 MONTHS
98	JK	357061	121	2.85	5.2	1.86	18	4	NO	YES	HYPERKALEMIA,AKI	EXPIRED	3.5 MONTHS
99	MK	343055	64	2.08	4.5	1.6	32	3	NO	NO	HYPERKALEMIA	NONE	6 MONTHS
100	RS	157581	124	3.9	5.9	3.92	16	4	NO	NO	HYPERKALEMIA	HYPERKALEMIA	4 MONTHS

Baba Farid University
of Health Sciences
Sadiq Road
Faridkot-151 203 (Pb). INDIA.
Phone : 01639-256232,256236
Tele/Fax : 01639-256235
Email – Examination@bfuhs.ac.in

No. BFUHS/2K21p-TH/ 1145

Date 2/2/2021

The Principal,
DMC, Ludhiana

Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of Dr Gaurav Singla , a student of your college for DM Nephrology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Pattern of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and outcomes of their use in ckd patients at a tertiary care hospital

Supervisor
Dr. Vikas Makkar
Prof. & Head,
Dept. of Nephrology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Bishav Mohan
Prof.,
Dept. of Cardiology,
DMCH, Ludhiana.

Dr. Simran Kaur
Asst. Prof.,

The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Opth)
Controller of Examinations

Note :
i. If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.

PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

NEPHROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

MARCH, 2020

DR. GAURAV SINGLA

DEPARTMENT OF NEPHROLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL
For the degree of	D.M Nephrology
Name of the candidate	Dr. Gaurav Singla
Supervisor	Dr. Vikas Makkar, Professor & Head, Department of Nephrology, DMCH, Ludhiana
Co-supervisor	Dr. Bishav Mohan, Professor, Department of Cardiology, DMCH, Ludhiana Dr. Simran Kaur, Assistant Professor, Department of Nephrology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) are indicated for use in CKD patients with hypertension and proteinuria/albuminuria. Definitive data on whether to continue use of ACE inhibitors (ACEis) and angiotensin-II receptor blockers (ARBs)in patients with chronic kidney disease (CKD) is lacking.

Aim of Study: To study the Pattern of use and the Outcomes of use of ACE inhibitors and ARB's in CKD patients

Materials & methods: During the study period CKD Stage 3-4 patients will be studied at time of enrollment regarding their Baseline parameters, indications for use of ACE inhibitors / ARBs if already taking before enrollment into the study, duration, dosage and frequency of drug usage. Those patients not taking ACE inhibitors or ARBs but are eligible as per the inclusion criteria in the study at the time of enrollment will be started on the ACE inhibitors or ARBs on the recommended dosage and frequency. Patients will be followed at regular intervals till 6 months after enrollment into the study.

Clinical Significance: To find the exact pattern of use and the outcomes in the form of tolerability to use of ACE inhibitors or ARB's in CKD patients. This study is being undertaken.

Keywords: ACE inhibitors, ARBs, CKD

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL"** exist in the Department of Nephrology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

Dr. Vikas Makkar
Professor & Head
Department of Nephrology
DMCH, Ludhiana

Co-Supervisor

Dr. Bishav Mohan
Professor
Department of Cardiology
DMCH, Ludhiana

Dr. Simran Kaur
Assistant Professor
Department of Nephrology
DMCH, Ludhiana

Head of the Department

Dr. Vikas Makkar
Professor & Head
Department of Nephrology
DMCH, Ludhiana

Place : Ludhiana

Date : 23/05/2020

APPROVAL PROFORMA
BYRESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. GauravSingla
Department	Nephrology
Topic of Thesis	PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL
Likely date of appearing in PG examination	MAY, 2022
Date of enrollment	11th September 2019
Name of Head of Department	Dr. Vikas Makkar
1) **Supervisor** 2) **Co-Supervisor**	Dr. Vikas Makkar Dr. Bishav Mohan Dr. Simran Kaur
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Jaspal Singh (Professor & Head, Surgery)	Mr. A K Jindal (Member, Ethics Committee)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Assistant Dean Academics)	Dr. Deepinder K Chhina (Professor & Head, Microbiology)
Dr. Rajoo Singh Chhina (Dean Academics)	Dr. Neena Sood (Professor & Head, Pathology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / ~~No~~

Dr. Sandeep Puri
Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes / No

Prof. Arvind Malhotra
Chairperson
Ethics Committee

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Gaurav Singla H. No B-XI-2799, New Grain Market Road, Barnala.
2	NAME OF THE INSTITUTE	Dayanand Medical College & Hospital, Ludhiana.
3	COURSE OF STUDY AND SUBJECT	D.M. Nephrology
4	DATE OF ADMISSION OF COURSE	11th September 2019
5	TITLE OF THE TOPIC	PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL

6. BRIEF RESUME OF THE INTENDED WORK

6.1NEED FOR THE STUDY

Chronic kidney disease (CKD) is a global health problem associated with considerable morbidity and mortality and despite advances in the treatment of end stage renal disease (ESRD) mechanisms to prevent and delay its progression are still being sought. CKD is defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated Glomerular filtration rate (GFR) < 60 ml/min/1.73m^2, that persists for more that three months.[1,2]

ACE/ARB therapy is a cornerstone of hypertension and proteinuria management in CKD. They have been shown to have apparently salutary effects on markers of kidney function. Given the change in the therapeutic landscape of hypertension and the public health burden of CKD, it seems reasonable to suggest that trends in ACE/ARB use in CKD population should be followed closely. Although blockade of the RAAS with ACE inhibitors, Ang II type1 receptor antagonists, or the combination of both should be part of every strategy to slow progression of renal disease, a better understanding of the novel aspects of the RAAS should contribute to the development of innovative strategies not only to completely halt progression but also to induce regression of human renal disease.[3] The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in many of the pathophysiological changes that lead to progression of renal disease. Traditionally RAAS was considered as an endocrine system and its principal role was to maintain blood pressure (BP). In recent years local RAAS has been described to operate independently from systemic and local angiotensin II (Ang II) in the kidney to contribute in hypertension and kidney damage.

The benefits of strict BP control in slowing kidney disease progression have been demonstrated in several clinical trials and the question whether specific agents like angiotensin converting enzyme antagonists (ACEIs) and angiotensin receptor blockers (ARBs) provide

renoprotective benefits beyond BP lowering is to be answered. Several studies support these agents reduce proteinuria and protect renal function, whereas the opposite is stated by others.[4] Definitive data on whether to continue use of ACE inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs)in patients with chronic kidney disease (CKD) is lacking.[5] At this time, it is difficult to prove that the renoprotective effects of renin-angiotensin-aldosterone system (RAAS) inhibitors are separate from their antihypertensive effects. ACE inhibitors and ARBs are indicated for use in CKD patients with hypertension and proteinuria/ albuminuria.[5] The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative *Clinical Practice Guidelines on Hypertension* currently state that with careful monitoring most patients with advanced CKD can continue taking ACEis/ARBs.[7] In a study to find the trends in Angiotensin-Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker Use among those with impaired kidney function in the United States, Murphy and others found that rates of ACE/ARB use increased in the early 2000s among United States adults with CKD, but for unclear reasons, use appeared to plateau in the ensuing decade. They stated that Research examining barriers to care and other factors is needed.[8] The need of this study was also based on the observation that data on Prevalence and practice of use of ACE Inhibitors and ARB's in CKD patients and outcomes of its use is not much available in Indian population. To find the exact barriers and the tolerability of CKD patients to use of these drugs, this study is being undertaken.

6.2 REVIEW OF LITERATURE

In a study by Maschio and others in 1996 to determine the effect of the angiotensin-converting–enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases. In a three-year trial involving 583 patients with renal insufficiency caused by various disorders, 300 patients received benazepril and 283 received placebo. The underlying diseases included glomerulopathies (in 192 patients), interstitial nephritis (in 105), nephrosclerosis (in 97), polycystic kidney disease (in 64), diabetic nephropathy (in 21), and miscellaneous or unknown disorders (in 104). The severity of renal insufficiency was classified according to the base-line creatinine clearance: 227 patients had mild insufficiency (creatinine clearance, 46 TO 60 ml per minute), and 356 had moderate insufficiency (creatinine clearance, 30 to 45 ml per minute). The primary end point was a doubling of the base-line serum creatine concentration or the need for dialysis. They Concluded that benazepril provides protection against the loss of renal function in patients with chronic renal insufficiency caused by various disorders. This protective effect was associated with a substantial decrease in blood pressure and urinary protein excretion.[9]

In a study by Hou and others in 2006, they assessed the efficacy and safety of benazepril in patients without diabetes who had advanced renal insufficiency. They enrolled 422 patients in a randomized, double-blind study. After an eight-week run-in period, 104 patients with serum creatinine levels of 1.5 to 3.0 mg per deciliter (group 1) received 20 mg of benazepril per day, whereas 224 patients with serum creatinine levels of 3.1 to 5.0 mg per deciliter (group 2) were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. All patients received conventional antihypertensive therapy. The primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease.

In their study they concluded that benazepril therapy was associated with a significant improvement in renal outcome and surpassed that attributable to blood-pressure control in patients without diabetes who had advanced renal dysfunction.[10]

In a study Kolesnyk et al in 2010, they found that drugs that inhibit the RAS are proven to be effective in the treatment of hypertension and heart failure. In patients with chronic kidney disease these medications appeared to bring benefit beyond their direct effects on the cardiovascular system, resulting in preservation of renal and peritoneal function and improved patient survival.[11]

In a study by Ahmed and others in 2012 to study the Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease.Of the 1665 patients (aged≥65 years) with systolic heart failure (ejection fraction<45%) and chronic kidney disease (estimated glomerular filtration rate<60 mL/min/1.73 m(2)), 1046 received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Propensity scores for the receipt of these drugs, estimated for each of the 1665 patients, were used to assemble a matched cohort of 444 pairs of patients receiving and not receiving these drugs who were balanced on 56 baseline characteristics. In their study they found that Discharge prescription of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with a significant modest reduction in all-cause mortality in older patients with systolic heart failure with chronic kidney disease, including those with more advanced chronic kidney disease.[12]

In a study by Miklos Z. Molnar and others in 2014, they conducted a study to assess the association between angiotensin-converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB) use and mortality in patients with chronic kidney disease.A logistic regression analysis was used to calculate the propensity of ACEI/ARB initiation in 141,413 U.S. veterans with nondialysis CKD who were previously unexposed to ACEI/ARB treatment.They examined the association of ACEI/ARB administration with all-cause mortality in patients matched by propensity scores using the Kaplan-Meier method and Cox models

in "intention-to-treat" analyses and in generalized linear models with binary outcomes and inverse probability of treatment weights in "as-treated" analyses. They found that in nondialysis-dependent patients with CKD, ACEI/ARB administration was associated with greater survival.[13]

In a study by Dattolo et al in 2016 to study the Conservative management of chronic kidney disease stage 5: role of angiotensin converting enzyme inhibitors. They tested the role of ACE-I in slowing the progression of renal damage in a real-world elderly population with CKD stage 5. They found that proteinuria independently predicts further renal damage progression even in end-stage renal disease patients not yet in dialysis. In cohort of elderly patients with very advanced CKD, ACE-I was effective in slowing down further renal damage progression.[14]

In a study by Frohlich Hanna and others in 2016 to study Long-term changes of renal function in relation to ace inhibitor/angiotensin receptor blocker dosing in patients with heart failure and chronic kidney disease. In this retrospective observational study, they identified 722 consecutive patients with systolic CHF, stable CKD stage III/IV (estimated glomerular filtration rate [eGFR] 15-60 mL min(-1) 1.73 m(-2)) and chronic ACEI/ARB treatment from the outpatient heart failure clinics at the Universities of Hull, UK, and Heidelberg, Germany. Change of renal function, worsening CHF, and hyperkalemia at 12-month follow-up were analyzed as a function of both baseline ACEI/ARB dose and dose change from baseline. In patients with systolic CHF and stable CKD stage III/IV, neither continuation of high doses of ACEI/ARB nor up-titration was related to adverse changes in longer-term renal function. Conversely, down-titration was not associated with improvement in eGFR. Use of high doses of ACEI/ARB and their up-titration in patients with CHF and CKD III/IV may be appropriate provided that the patient is adequately monitored.[15]

In a study by Lin et al in 2017 to study the Angiotensin receptor blockers are associated with lower mortality than ACE inhibitors in predialytic stage 5 chronic kidney disease: A nationwide study of

therapy with rennin angiotensin system blockade and their study demonstrated the difference in the effectiveness and safety between ACEIs, ARBs and dual RAS blockade therapy (ACEI plus ARB) in pre-dialytic stage 5 CKD patients. As compared with ARBs, dual blockade with ACEIs and ARBs showed a higher risk of death and composite endpoint of long-term dialysis or death in diabetic subgroup as well as a higher rate of hyperkalemia-associated hospitalization in non-diabetic subgroup, and ACEIs were associated with a higher risk of death, especially in diabetic subgroup. Monotherapy of RAS blockade, especially ARB, was more effective and safer than dual RAS blockade in pre-dialytic stage 5 CKD patients.[16]

In a study by Elaine Ku and others in 2018 todetermine patterns of antihypertensive agent use by stage of chronic kidney disease (CKD) and to evaluate the association between different classes of antihypertensive agents with nonrenal outcomes, especially in advanced CKD. They studied 3939 participants of the CRIC (Chronic Renal Insufficiency Cohort) study. Predictors were time-dependent angiotensin-converting enzyme inhibitor or angiotensin receptor blocker , β-blocker, and calcium channel blocker use (versus nonuse of agents in each class). Outcomes were adjudicated heart failure events or death. Adjusted Cox models were used to determine the association between predictors and outcomes. They also examined whether the associations differed based on the severity of CKD (early [stage 2-3 CKD] versus advanced disease [stage 4-5 CKD]). During median follow-up of 7.5 years, renin-angiotensin-aldosterone system inhibitor use plateaued during CKD stage 3 (75%) and declined to 37% by stage 5, while β-blocker, calcium channel blocker, and diuretic use increased steadily with advancing CKD. Renin-angiotensin-aldosterone system inhibitor use was associated with lower risk of heart failure (hazard ratio, 0.79; 95% confidence interval, 0.67-0.97) and death (hazard ratio, 0.78; 95% confidence interval, 0.67-0.90), regardless of severity of CKD . Calcium channel blocker use was not associated with risk of heart failure or death, regardless of the severity of CKD . β-Blocker use was associated with higher risk of heart failure (hazard

ratio, 1.62; 95% confidence interval, 1.29-2.04) and death (hazard ratio, 1.22; 95% confidence interval, 1.03-1.43), especially during early CKD (P<0.05 for interaction). They Concluded in their study that Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use decreased, while use of other agents increased with advancing CKD. Use of agents besides angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be associated with suboptimal outcomes in patients with CKD.[17]

In a study conducted by Yao Qiao et al in 2019 to assess the patterns of ACE-I/ARBdiscountinuation in the setting of chronic kidney disease progression and dentified incident ACE-I/ARB users with a baseline estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2 and without end-stage renal disease in the Geisinger Health System between January 1, 2004, and December 31, 2015. They investigated the associations of CKD stage, hospitalizations with and without acute kidney injury (AKI), serum potassium, bicarbonate level, thiazide, and loop diuretic use with ACE-I/ARB discontinuation. It was found that discontinuation of ACE-I/ARB was common, particularly in patients with lower eGFR. Hyperkalemia, hypotension, low bicarbonate level, and hospitalization (AKI-related, in particular) were associated with a higher risk of ACE-I/ARB discontinuation.[18]

In a study conducted by Daniel P. Murphy, Paul E. Drawz, and Robert N. Foley in 2019, they examined ACE/ARB trends from 1999 to 2014 among 38,885 adult National Health and Nutrition Examination Survey participants with creatinine-based eGFR<60 ml/min per 1.73 m^2 or urinary albumin-to-creatinine ratio ≥ 30 mg/g. Of 7085 participants with CKD, 34.9% used an ACE/ARB. Across four eras studied, rates of use rose significantly (rates were 25.5% in 1999–2002, 33.3% in 2003–2006, 39.0%in 2007–2010, and 40.1% in 2011–2014) but appeared to plateau after 2003.and it was found that in adults with CKD, although use of ACE/ARB increased between 1999 and 2014, it appeared to plateau after 2003, with less than one half of the CKD population using an ACE/ARB.[8]

In a very recent study by Qiao et al in 2020To investigate the association of ACE-I or ARB therapy discontinuation after eGFR decreases to below 30 mL/min/1.73 m^2 with the risk of mortality, major adverse cardiovascular events (MACE), and end-stage kidney disease (ESKD) conducted retrospective, propensity score-matched cohort study included 3909 patients from an integrated health care system that served rural areas of central and northeastern Pennsylvania. Patients who initiated ACE-I or ARB therapy from January 1, 2004, to December 31, 2018, and had an eGFR decrease to below 30 mL/min/1.73 m^2 during therapy were enrolled, with follow-up until January 25, 2019. Individuals were classified based on whether they discontinued ACE-I or ARB therapy within 6 months after an eGFR decrease to below 30 mL/min/1.73 m^2.found a higher risk of mortality and MACE associated with ACE-I or ARB therapy discontinuation after an eGFRdecreaseto below 30 mL/min/1.73 m2 but no significant difference in the risk of ESKD. Similar patterns held for individuals with a40% or greater decrease in eGFR. Their findings suggest that continuing ACE-I or ARB therapy in patients with declining kidney function may provide cardiovascular and survival benefits without excess risks of ESKD.[19]

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To study the Pattern of use of ACE inhibitors and ARB's in CKD Patients
2. To study the Outcomes of use of ACE inhibitors and ARB's in CKD patients

7.0 MATERIALS AND METHODS

7.1 Source of Data: This is a prospective observational study done on Patients attending OPD, admitted patients from Department of Nephrology and Cardiology during the study duration from March 1st 2020 to 28th Feb 2021.

7.2 METHODS OF COLLECTION OF DATA

INCLUSION CRITERIA:

Patients above the age of 18 yrs with CKD Stage 3-4 with informed consent will be included those having one of the following:

- Patients with Diabetic kidney disease
- Non Diabetic Proteinuric chronic kidney disease (defined as urine protein excretion greater than 500 mg/day)
- A diagnosis of CHF based on relevant symptoms and signs supported by objective evidence of substantial abnormalities of cardiac function on imaging or invasive hemodynamics

EXCLUSION CRITERIA:

- Patients who refuse to give consent
- Estimated GFR (eGFR) <15 mL/min/1.73m² at baseline
- Patients with age < 18 and > 65 years
- Patients who are pregnant
- Cardiac decompensation requiring inotropic support in the previous 3 months
- Requirement of renal replacement therapy
- A history of primary or severe concomitant valve disease.
- A history of angioedema/cough/allergy previously on use of ACE inhibitors or ARB's
- Serum potassium > 5.5 meq/l at the time of enrolment into the study
- Any contraindication to use of ACE inhibitors or ARB's

A predefined proforma will be used to collect the whole data. After an informed consent, relevant history taking and physical examination will be done. Relevant investigations related to will be done, which includes

- Complete Hemogram
- ESR
- Serum creatinine, urea & electrolytes,
- Serum calcium and phosphorus
- Serum alkaline phosphatase
- Uric acid
- Liver function tests
- Urine routine examination
- Spot Urine protein:creatinine ratio
- 24 hour urinary proteins
- USG KUB.
- Chest X ray
- 2D-Echocardiography
- Renal Doppler study

CKD is defined according to the KDIGO practice guidelines [20] as abnormalities of kidney structure or function present for at least 3 months which can be either Markers of kidney damage or low glomerular filtration rate (GFR) < 60 ml/min/1.73m^2. GFR will be calculated as per The CKD-EPI equation, as currently recommended by the international consensus KDIGO 2012 guidelines.

Patients of CKD will be staged into following categories.

Categories	**GFR (mL/min/1.73 m2)**
G1	≥ 90 Normal or high
G2	60-89 Mildly decreased
G3a	45-59 Mildly to moderately decreased
G3b	30-44 Moderately to severely decreased
G4	15-29 Severely decreased
G5	< 15 Renal failure

Based on the relevant investigations and GFR, those patients found eligible will be studied at time of enrollment regarding the Baeline parameters, drug history, indications for use of ACE inhibitors / ARBs. If patient is already taking ACE inhibitors or ARB's before enrollment

into the study, information will be collected about drug use, duration, dosage, compliance to the treatment and frequency of drug usage. Those patients not taking ACE inhibitors or ARBs but are eligible as per the inclusion criteria in the study at the time of enrollment will be assessed for their hydration status, additional drug intake like diuretics or NSAIDs. After proper hydration status has been confirmed, patients will be started on the ACE inhibitors or ARBs on the recommended dosage and frequency. Medication and choice between ACE inhibitors or ARBs will be at the discretion of the treating physician with respect to guideline recommended drugs. Target doses and dose equivalents for ACEIs and ARBs will be as Recommended guidelines.

Monitoring and Follow Up

Patients will be monitored frequently for side effects at regular intervals.

Interval for the further monitoring for side effects with measurements of Blood Pressure, GFR, Serum potassium, 24 hour urinary proteins/ UPCR after initiation of drug or enrolment into the study or after any Change in Dose of Drug follow up will be done within 1 week.

Subsequent follow up to monitor the side effects and if dose is stable will be done at every 1-2 month with measurements of Blood Pressure, GFR ,Serum potassium, 24 houurinary proteins/UPCR, till the completion of follow up at end of 6 months.

Duration Study: March 1st 2020 to 28th Feb 2021.

Type of study: Prospective observational study

Outcome Parameters

Outcome of our study will be assessed in the form of tolerability of the Patient to the treatment at the end of 6 month follow up.

Outcome status will be determined at the follow-up visits and verified either through electronic hospital records or telephone calls to the patients' and their attendants.

7.3 STATISTICAL ANALYSIS

Data will be described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. A probability value (p value) less than

0.05 will be considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

No. Patients included in the study will have to undergo hematological, biochemical or radiological investigations as per the protocol. For this patients included in the study will be informed regarding their inclusion and written informed consent will be taken for all the patients included in the study.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

NA

8.0 LIST OF REFERENCES

1. KDOQI Clinical Practice Guidelines and Clinical Practice. Recommendations for Anemia in Chronic Kidney Disease. Am. J. Kidney Dis. 2006;47:S11-145.
2. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international. 2005;67:2089-100.
3. Rüster C, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. J Am SocNephrol. 2006;17:2985-91.
4. Baltatzi M, SavopoulosCh, Hatzitolios A. Role of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension of chronic kidney disease and renoprotection: Hippokratia. 2011;15:27-32.
5. Ahmed A, Jorna T, Bhandari S. Should we STOP angiotensin converting enzyme inhibitors/angiotensin receptor blockers in advanced kidney disease? Nephron. 2016;133:147-58.
6. Bhandari S, Ives N, BrettellEA, Valente M, Cockwell P, Topham PS, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. Nephrol Dial Transplant. 2016;31:255-61.
7. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43:S1-290.
8. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use among those with impaired kidney function in the United States. J Am SocNephrol. 2019;30:1314-21.
9. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med.1996;334:939-45.

10. HouFF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med.2006;354:131-40.
11. Kolesnyk I, Struijk DG, Dekker FW, Krediet RT. Effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with chronic kidney disease. Neth J Med. 2010;68:15-23.
12. Ahmed A, Fonarow GC, Zhang Y, Sanders PW, Allman RM, Arnett DK, Feller MA, Love TE, AbanIB, Levesque R, et al. Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease. Am J Med. 2012;125:399–410.
13. Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. Journal of the American College of Cardiology. 2014;63:650-8.
14. Dattolo PC, Gallo P, Michelassi S, et al. Conservative management of chronic kidney disease stage 5: role of angiotensin converting enzyme inhibitors. J Nephrol. 2016;29:809–15.
15. Fröhlich H, Nelges C, Täger T, Schwenger V, Cebola R, Schnorbach J, et al. Long-Term Changes of Renal Function in Relation to Ace Inhibitor/ARB Dosing in Patients with Heart Failure and Chronic Kidney Disease.Am Heart J.2016;178:28-36.
16. Lin CC, Wu YT, Yang WC, Tsai MJ, Liu J, Yang CY, et al. Angiotensin receptor blockers are associated with lower mortality than ACE inhibitors in predialytic stage 5 chronic kidney disease: a nationwide study of therapy with renin-angiotensin system blockade. PLoS One. 2017;12:e0189126.
17. Ku E, McCulloch CE, Vittinghoff E, Lin F, Johansen KL. Use of antihypertensive agents and association with risk of adverse outcomes in chronic kidney disease: focus on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.J Am Heart Assoc. 2018;7:e009992.

18. Qiao Y, Shin JI, Sang Y, Inker LA, Secora A, Luo S, et al. Discontinuation of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Kidney Disease. Mayo Clin Proc. 2019;94:2220-2229.
19. Qiao Y, Shin JI, Chen TK, Inker LA, Coresh J, Alexander GC, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate JAMA Intern Med. 2020 Mar 9. [Epub ahead of print]
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Inter Suppl 2013;3:1-150.

PROFORMA

Sr. No.

Name Age/ Sex Cr No.

Indoor/outdoor

Father/ Husband Name

Address

Phone No.

Date of enrollment

Diagnosis

CKD stage

Cause of CKD

Duration since diagnosis

Comorbidities

Chief Complaints

Past History

Family History

Personal History

Dietary habits

Smoking

Duration /Number of Pack Year

Signature of Candidate **Signature of Supervisor**

General Physical Examination

Weight	Height	BMI
Blood Pressure	Pulse	Temperature
Pallor	Icterus	Clubbing
Cyanosis	Jugular venous Pressure	Lymphadenopathy

Dermatological examination

Systemic Examination

Chest

CVS

P/A

CNS

Signature of Candidate **Signature of Supervisor**

Investigations

Date	Baseline/ At time of enrolment into study
Urinalysis	
24 hour Urinary Proteins	
UPCR	
Haematology	
Hb (g/dl)	
TLC(cells/µl)	
DLC	
Platelets (cells/µl)	
ESR	
Blood Biochemistry	
Urea(mg/dl)	
Creatinine(mg/dl)	
GFR (mL/min/1.73 m2)	
Sodium(meq/l)	
Potassium(meq/l)	
Calcium(mg/dl)	
Phosphorus(mg/dl)	
Albumin(g/dl)	
Uric Acid(mg/dl)	
Alk.Phosphatase(U/L)	
SGOT/PT(U/L)	
GGT(U/L)	
TB/DB(mg/dl)	
Total Protein (g/dl)/Albumin	
iPTH(pg/ml)	
25 (OH) vit D(ng/ml)	
Seum Fe(µg/dl)	
Ferritin(ng/ml)	
TIBC(mcg/dl)	
T SAT(%)	
Blood Sugar - Random(mg/dl) - Fasting(mg/dl) - HbA1c(%)	
USG KUB	
2D Echo (LVEF %)	

Signature of Candidate **Signature of Supervisor**

CXR-PA view

ECG

HbsAg

Anti-HIV 1 and 2

Anti-HCV

Ultrasound Abdomen(wherever required)

Treatment with ACE INHIBITORS or ARB's

Indication of ACE/ARB's

Whether taking ACE Inhibitors or ARB's at time of enrolment into study

If yes which

Drug name

Dosage

Frequency

Duration of drug usage

Compliance to treatment

Any Compication Previously on use of drug

if not previously taking,

Drug prescribed

Dosage

Frequency

Signature of Candidate **Signature of Supervisor**

Follow up

Follow up	Date	BP	Urea (mg/dl)	Creatinine (mg/dl)	Serum Pottasium	GFR	24 Hour Urinary Proteins	UPCR	Change in Drug Dosage if any
Follow up-1									
Follow up-2									
Follow up-3									
Follow up-4									

ADVERSE EVENT

- Dropouts
- Lost follow up
- Change or stoppage of drug
- Worsening CHF / NYHA class
- Significant hyperkalemia (serum potassium >5.5 mmol/L)
- Any other adverse event
- Hospitalisation
- **Death**
  - Cardiovasscular cause
  - Sudden death
  - Infections
  - Others causes

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o,W/o,S/o.....
am willing to participate in the study **"PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL"**
The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....
Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL"**में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक केहस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____"

PATTERN OF USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS AND OUTCOMES OF THEIR USE IN CKD PATIENTS AT A TERTIARY CARE HOSPITAL" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ